Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiff
Actelion Pharmaceuticals Ltd

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ACTELION PHARMACEUTICALS LTD, Plaintiff, v. LAURUS LABS LIMITED and PHARMAQ, INC., Defendants.	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Actelion Pharmaceuticals Ltd ("Actelion" or "Plaintiff"), for its Complaint against Defendants Laurus Labs Limited ("Laurus") and PharmaQ, Inc. ("PharmaQ") (collectively, "Defendants"), hereby alleges as follows:

THE PARTIES

1. Plaintiff Actelion Pharmaceuticals Ltd is a Swiss corporation having a primary place of business at Gewerbestrasse 16, CH-4123 Allschwil, Switzerland.

2. Upon information and belief, Defendant Laurus Labs Limited is an entity organized and existing under the laws of India, with a principal place of business at Serene Chambers, Road No. 7, Banjara Hills, Hyderabad-500 034, India.

3. Upon information and belief, Defendant PharmaQ, Inc. is an entity organized and existing under the laws of New Jersey, with a principal place of business at Waterview Plaza, 2001 Route 46, Suite 105, Parsippany, New Jersey 07054.

JURISDICTION AND VENUE

4. This is a civil action for infringement of United States Patent No. 7,094,781 ("the '781 patent" or "the patent-in-suit"). This action arises under the patent laws of the United States, 35 U.S.C. §§ 100 *et seq*., as well as the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 2202, and 35 U.S.C. § 271. This Court may declare the rights and other legal relations of the parties under 28 U.S.C. §§ 2201-02 because this case is an actual controversy within the Court's jurisdiction.

6. Upon information and belief, Laurus maintains a regular place of business in New Jersey through its wholly-owned subsidiary, Laurus Generics Inc., having a principal place of business located at 400 Connell Drive, Suite 5200, Berkeley Heights, New Jersey 07922.

7. Upon information and belief, Laurus directly and/or through its subsidiaries, agents, and/or alter egos, develops, manufactures, markets, sells, and/or imports generic versions of branded pharmaceutical products throughout the United States, including in this Judicial District.

8. Upon information and belief, PharmaQ is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0100536377.

9. Upon information and belief, PharmaQ provides services to drug companies with respect to their pharmaceutical products in the United States, including in this Judicial District.

10. Upon information and belief, PharmaQ is an agent for Laurus with regard to Abbreviated New Drug Application ("ANDA") No. 211120, for which Laurus and PharmaQ have jointly sought approval from the United States Food and Drug Administration ("FDA").

11. Laurus and PharmaQ sent a letter dated August 26, 2020 ("August 26, 2020 Notice Letter") to Actelion, stating that Laurus filed ANDA No. 211120, seeking approval from the FDA to commercially manufacture, use, or sell generic macitentan 10 mg oral tablets ("the ANDA Product") in the United States (including, upon information and belief, in the State of New Jersey) prior to the expiration of the '781 patent.

12. The August 26, 2020 Notice Letter represented that ANDA No. 211120 included a certification under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) with respect to the '781 patent ("Paragraph IV Certification"). The August 26, 2020 Notice Letter also included an Offer of Confidential Access ("OCA") to ANDA No. 211120, which states that "this Offer of Confidential Access shall be governed by the laws of the State of New Jersey." On or about August 27, 2020, Actelion received the August 26, 2020 Notice Letter.

13. Upon information and belief, Laurus, together with its agent PharmaQ, filed or caused to be filed ANDA No. 211120 with the FDA.

14. This Court has personal jurisdiction over Laurus because, *inter alia*, Laurus: (1) maintains a regular place of business in New Jersey through its wholly-owned subsidiary Laurus Generics Inc.; (2) has purposely availed itself of the privilege of doing

business in New Jersey, including directly and/or indirectly through its subsidiaries, agents, and/or alter egos; (3) maintains pervasive, continuous, and systematic contacts with New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical products in New Jersey directly or indirectly through its subsidiaries, agents, and/or alter egos; (4) upon information and belief, derives substantial revenue from the sale of its products in New Jersey, including directly or indirectly through its subsidiaries, agents, and/or alter egos; and (5) upon information and belief, intends to, directly or indirectly through its subsidiaries, agents, and/or alter egos, market, sell, or distribute the ANDA Product in New Jersey.

15. This Court also has personal jurisdiction over Laurus because, *inter alia*, Laurus, directly and/or indirectly through its subsidiaries, agents, and/or alter egos, has committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement, including acts in New Jersey, including by sending the August 26, 2020 Notice Letter to New Jersey, that have led to foreseeable harm and injury to Actelion in New Jersey.

16. This Court also has personal jurisdiction over Laurus because, *inter alia*, Laurus has availed itself of the legal protections of the State of New Jersey by offering Actelion access to ANDA No. 211120 as governed by the laws of the State of New Jersey.

17. This Court also has personal jurisdiction over Laurus because, *inter alia*, Laurus has availed itself of the legal protections of the State of New Jersey by previously consenting to personal jurisdiction in this Judicial District. *E.g.*, *Janssen Prods. L.P., et al. v. Dr. Reddy's Labs., Inc., Laurus Labs Ltd., PharmaQ, Inc., et al.*, Civil Action No. 18-9655 (D.N.J.); *Mitsubishi Tanabe Pharma Corp., et al. v. MSN Labs. Private Ltd., Laurus Labs. Ltd., et al.*, Civil Action No. 17-5302 (D.N.J.).

18. Alternatively, this Court may exercise jurisdiction over Laurus pursuant to Fed. R. Civ. P. 4(k)(2) because, *inter alia*, (1) Actelion's claims arise under federal law; (2) Laurus is a foreign entity not subject to personal jurisdiction in any state's court of general jurisdiction; and (3) Laurus has sufficient contacts with the United States as a whole, including, but not limited to, by submitting various ANDAs to the FDA and manufacturing, importing, offering to sell, or selling pharmaceutical products throughout the United States, such that this Court's exercise of jurisdiction over Laurus satisfies due process.

19. This Court has personal jurisdiction over PharmaQ because, *inter alia*, PharmaQ: (1) is an entity organized and existing under the laws of New Jersey; (2) has a principal place of business in New Jersey; (3) has purposely availed itself of the privilege of doing business in New Jersey, including by, *inter alia*, registering with the State of New Jersey's Division of Revenue and Enterprise Service to do business in New Jersey under entity ID No. 0100536377; and (4) maintains pervasive, continuous, and systematic contacts with New Jersey.

20. This Court also has personal jurisdiction over PharmaQ because, *inter alia*, PharmaQ has committed, aided, abetted, contributed to, and/or participated in the commission of acts of patent infringement, including acts in New Jersey, including by sending the August 26, 2020 Notice Letter to New Jersey, that have led to foreseeable harm and injury to Actelion in New Jersey.

21. This Court also has personal jurisdiction over PharmaQ because, *inter alia*, PharmaQ has availed itself of the legal protections of the State of New Jersey by previously consenting to personal jurisdiction in this Judicial District. *E.g.*, *Janssen Prods. L.P., et al. v.*

Dr. Reddy's Labs., Inc., Laurus Labs Ltd., PharmaQ, Inc., et al., Civil Action No. 18-9655 (D.N.J.).

22. Venue is proper in this Court as to Laurus under 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b) because, *inter alia*, Laurus is a foreign entity and may be sued in any judicial district in the United States in which Laurus is subject to the court's personal jurisdiction. Venue is proper for the additional reasons set forth above and for other reasons that will be presented to the Court if such venue is challenged.

23. Venue is proper in this Court as to PharmaQ under 28 U.S.C. §§ 1391(b), (c), and/or (d), and 1400(b) because, *inter alia*, PharmaQ is an entity organized and existing under the laws of New Jersey, has a principal place of business in New Jersey, and has committed and will commit further acts of infringement in this Judicial District. Venue is proper for the additional reasons set forth above and for other reasons that will be presented to the Court if such venue is challenged.

THE PATENT-IN-SUIT

24. Actelion holds approved New Drug Application ("NDA") No. 204410, under which the FDA granted approval on October 18, 2013 for macitentan 10 mg oral once-a-day tablets, marketed in the United States under the trade name OPSUMIT®.

25. OPSUMIT® (macitentan), approved in NDA No. 204410, is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH.

26. Actelion owns the '781 patent, titled "Sulfamides and Their Use as Endothelin Receptor Antagonists." The '781 patent duly and legally issued on August 22, 2006. A copy of the '781 patent is attached as Exhibit A.

27. Pursuant to 21 U.S.C. § 355(b)(l), the '781 patent is listed in the FDA publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book"), as covering Actelion's OPSUMIT® brand macitentan tablets.

ACTS GIVING RISE TO THE ACTION

28. Upon information and belief, Laurus and PharmaQ have submitted ANDA No. 211120 to the FDA, seeking FDA approval for the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the ANDA Product.

29. Upon information and belief, prior to about October 18, 2017, Laurus was aware of the '781 patent.

30. Upon information and belief, prior to about October 18, 2017, PharmaQ was aware of the '781 patent.

31. Upon information and belief, on or about October 18, 2017, Laurus and PharmaQ submitted ANDA No. 211120 to the FDA.

32. Upon information and belief, when Laurus and PharmaQ submitted ANDA No. 211120 to the FDA on or about October 18, 2017, the ANDA included a certification under § 505(j)(2)(A)(vii)(III) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) with respect to the '781 patent ("Paragraph III Certification").

33. Upon information and belief, at the time Laurus and PharmaQ submitted the Paragraph III Certification, they did not possess an opinion supported by facts and law that the '781 patent was invalid.

34. Upon information and belief, at some time between about October 18, 2017 and August 26, 2020, Laurus and PharmaQ converted their Paragraph III Certification to the Paragraph IV Certification.

35. Upon information and belief, at some time prior to about August 26, 2020, Laurus was aware of the Consent Judgment (D.I. 145) in *Actelion Pharmaceuticals Ltd v. Zydus Pharmaceuticals (USA) Inc., et al.*, Civil Action No. 18-1397 (FLW)(LHG) (D.N.J.), in which Amneal Pharmaceuticals LLC admitted that the claims of the '781 patent are valid and enforceable.

36. Upon information and belief, at some time prior to about August 26, 2020, Laurus was aware of the Consent Judgment (D.I. 44) in *Actelion Pharmaceuticals Ltd v. Aurobindo Pharma USA Inc., et al.*, Civil Action No. 19-15437 (FLW)(LHG) (D.N.J.), in which Aurobindo Pharma USA Inc. and Aurobindo Pharma Limited admitted that the claims of the '781 patent are valid and enforceable.

37. Upon information and belief, Laurus is presently aware of the Consent Judgment (D.I. 169) in *Actelion Pharmaceuticals Ltd v. Zydus Pharmaceuticals (USA) Inc., et al.*, Civil Action No. 18-1397 (FLW)(LHG) (D.N.J.).

38. Separate and apart from certain contentions regarding patent validity, the August 26, 2020 Notice Letter does not identify any factual basis for, or any opinion of, noninfringement of Claim 11 of the '781 patent.

39. The product for which Laurus and PharmaQ seek FDA approval in ANDA No. 211120 includes macitentan as the active ingredient.

40. The chemical name of the compound macitentan is one of the chemical names recited in Claim 11 of the '781 patent.

41. Laurus, together with its agent PharmaQ, did not comply with its affirmative duty of care in making the Paragraph IV Certification with respect to the '781 patent under *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1347-48 (Fed. Cir. 2000).

42. On September 9, 2020, Actelion sent Laurus proposed terms for an OCA to ANDA No. 211120, and requested a response again on September 15, 2020, and on September 29, 2020. As of the date that this Complaint was filed, Laurus has not agreed to an OCA or provided Actelion with access to ANDA No. 211120.

43. Actelion commenced this action within 45 days of the date of receipt of the August 26, 2020 Notice Letter.

INFRINGEMENT BY LAURUS AND PHARMAQ

44. Actelion re-alleges paragraphs 1-43 as if fully set forth herein.

45. By seeking approval of ANDA No. 211120 to engage in the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the ANDA Product prior to the expiration of the '781 patent, Laurus and PharmaQ have infringed one or more claims of the '781 patent under 35 U.S.C. § 271(e)(2)(A).

46. Laurus and its agent PharmaQ are jointly and severally liable for infringement of the '781 patent under 35 U.S.C. § 271(e)(2)(A).

47. Upon information and belief, Laurus and PharmaQ were aware that the submission of ANDA No. 211120 that included the Paragraph IV Certification to the FDA constituted an act of infringement of one or more claims of the '781 patent.

48. Actelion is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of the approval of ANDA No. 211120 be a date that

is not earlier than the expiration date of the '781 patent, or any later expiration of any patent term extension or exclusivity for the '781 patent to which Actelion is or becomes entitled.

49. If Laurus and/or PharmaQ commercially manufacture, use, offer to sell, or sell within the United States, and/or import into the United States, the ANDA Product prior to the expiration of the '781 patent, Laurus and PharmaQ would further infringe one or more claims of the '781 patent under 35 U.S.C. §§ 271(a), (b), (c), and/or (g).

50. Laurus and its agent PharmaQ are jointly and severally liable for infringement of the '781 patent under 35 U.S.C. §§ 271(a), (b), (c), and/or (g).

51. Upon information and belief, Laurus and PharmaQ are aware that the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of the ANDA Product before the expiration of the '781 patent would constitute an act of infringement of one or more claims of the '781 patent.

52. Actelion is entitled to a declaration that, if Laurus and/or PharmaQ commercially manufacture, use, offer for sale, or sell the ANDA Product within the United States, import the ANDA Product into the United States, and/or induce or contribute to such conduct, Laurus and PharmaQ will infringe one or more claims of the '781 patent under 35 U.S.C. §§ 271(a), (b), (c), and/or (g).

53. Actelion will be irreparably harmed by Laurus's and PharmaQ's infringing activities unless those activities are enjoined by this Court. Actelion does not have an adequate remedy at law.

54. This is an exceptional case based on, *inter alia*, Laurus's and PharmaQ's failure to comply with their affirmative duty of care in converting their Paragraph III

Certification to a Paragraph IV Certification and propagating invalidity defenses that they know or have reason to know are lacking in an objective good-faith basis in fact and law.

PRAYER FOR RELIEF

WHEREFORE, Actelion requests that the Court grant the following relief:

A. A Judgment decreeing that Laurus and PharmaQ have infringed one or more claims of the '781 patent by submitting ANDA No. 211120 that included the Paragraph IV Certification;

B. A permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) or 35 U.S.C. § 283 restraining and enjoining Laurus and PharmaQ, their directors, officers, agents, attorneys, affiliates, divisions, successors and employees, and those acting in concert with Laurus and/or PharmaQ, from infringing one or more claims of the '781 patent by the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of any drug product claimed in the '781 patent;

C. An Order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 211120 be a date that is not earlier than the expiration date of the '781 patent, or any later expiration of any patent term extension or exclusivity for the '781 patent to which Actelion is or becomes entitled;

D. An award of monetary relief to the extent Laurus and/or PharmaQ commercially manufacture, use, offer for sale, or sell within the United States, or import into the United States, any product that infringes, induces, or contributes to the infringement of one or more claims of the '781 patent within the United States prior to the expiration of the '781 patent, including any later expiration of any patent term extension or exclusivity for the patent to which

Actelion is or becomes entitled, and that any such monetary relief be awarded to Actelion with prejudgment interest;

E. An Order be entered that this case is exceptional, and that Actelion is entitled to reasonable attorneys' fees pursuant to 35 U.S.C. § 285; and

F. Such other and further relief as the Court may deem just and proper.

Dated: October 5, 2020

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiff
Actelion Pharmaceuticals Ltd

Of Counsel:

Bruce M. Wexler
Preston K. Ratliff II
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter in controversy involves the same plaintiff and same patent (United States Patent No. 7,094,781) that were at issue in the matters captioned *Actelion Pharmaceuticals Ltd v. Zydus Pharmaceuticals (USA) Inc., et al.*, Civil Action No. 18-1397 (FLW)(LHG) (D.N.J.) and *Actelion Pharmaceuticals Ltd v. Aurobindo Pharma USA Inc., et al.*, Civil Action No. 19-15437 (FLW)(LHG) (D.N.J.), which were filed on January 31, 2018 and July 16, 2019, respectively. Those matters were dismissed by the Hon. Freda L. Wolfson, U.S.D.J. on September 22, 2020 and July 15, 2020, respectively.

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: October 5, 2020

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiff
Actelion Pharmaceuticals Ltd

Of Counsel:

Bruce M. Wexler
Preston K. Ratliff II
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000

EXHIBIT A

US007094781B2

(12) **United States Patent**
Bolli et al.

(10) **Patent No.: US 7,094,781 B2**
(45) **Date of Patent: Aug. 22, 2006**

(54) **SULFAMIDES AND THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS**

(75) Inventors: **Martin Bolli**, Allschwil (CH); **Christoph Boss**, Allschwil (CH); **Walter Fischli**, Allschwil (CH); **Martine Clozel**, Saint-Louis (FR); **Thomas Weller**, Binningen (CH)

(73) Assignee: **Actelion Pharmaceuticals Ltd.**, (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 312 days.

(21) Appl. No.: **10/433,041**

(22) PCT Filed: **Dec. 4, 2001**

(86) PCT No.: **PCT/EP01/14182**

§ 371 (c)(1),
(2), (4) Date: **May 27, 2003**

(87) PCT Pub. No.: **WO02/053557**

PCT Pub. Date: **Jul. 11, 2002**

(65) **Prior Publication Data**

US 2004/0077670 A1 Apr. 22, 2004

(30) **Foreign Application Priority Data**

Dec. 18, 2000 (EP) PCT/EP00/12890

(51) **Int. Cl.**
C07D 401/04 (2006.01)
C07D 239/47 (2006.01)
A61K 31/506 (2006.01)

(52) **U.S. Cl.** **514/235.8**; 514/255.05; 514/269; 544/123; 544/296; 544/319

(58) **Field of Classification Search** 544/123, 544/296, 319; 514/235.8, 255.05, 269
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,233,294 A 11/1980 Maurer et al.

FOREIGN PATENT DOCUMENTS

EP	0 526 708 A1	2/1993
EP	0 633 259 A1	1/1995
EP	0 657 548 A1	6/1995
EP	0 743 307 A1	11/1996
EP	0 882 719 A1	12/1998
EP	0 959 072 A1	11/1999
WO	WO 96/16963	6/1996
WO	WO 96/19459	6/1996
WO	WO 00/42035	7/2000
WO	WO 01/17976 A1	3/2001
WO	WO 01/46156 A1	6/2001
WO	WO 01/81335 A1	11/2001
WO	WO 01/81338 A1	11/2001

OTHER PUBLICATIONS

Simone, Oncology: Introduction, Cecil Textbook of Medicine, 20th Edition, vol. 1, pp. 1004-1010, 1996.*
Rubanyi et al., Endothelins: Molecular Biology, Biochemistry, Pharmacology, Physiology, and Pathophysiology, Pharmacological Reviews, vol. 46, No. 3, pp. 325-415, 1994.*
Neidhart, W., et al., Discovery of RO 48-5695: A Potent Mixed Endothelin Receptor Antagonist Optimized from Bosantan, Bioorganic & Medical Chemistry Letters, 7(17):2223-2228, 1997.
Gohring, W., et al., Development of a Process to Prepare 2-Cyanopyimidine on Commercial Scale, Chimia, 50:538-543, Nov. 1996.
Nugent, R., et al., Pyrimidine Thioethers: A Novel Class of HIV-1 Reverse Transcriptase Inhibitors with Activity Against BHAP-Resistant HIV, J. Med. Chem., 41:3793-3803.1998.
March, Jerry, Advanced Organic Chemistry, Fourth Edition, p. 499 and references cited therein, 1992.
Kohara, Y., et al., Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres, J. Med. Chem., 39:5228-5235, 1996.
Graf, R., Chem. Ber., 92:509-513, 1959.
Weiss, G., et al., Liebigs Ann. Chem., 729:40-51, 1969.
Kloek, J., et al., An Improved Synthesis of Suffamoyl Chlorides, J. Org. Chem., 41(25):4028-4029, 1976.
Dickinson, R., et al., Thromboxane Modulating Agents. 3. 1H-Imidazol-1-ylalkyl-and -3-Pyridinylalkyl-Substituted 3-[2-(Arylsulfonyl)amino)etthyl]benzenepropanoic Acid Derivatives as Dual Thromboxane Synthase Inhibitor/Thromboxane Receptor Antagonists, J. Med. Chem., 40:3442-3452, 1997.
Cohen, E., et al., Sulfamoyl Chloride, Sulfamides and Sulfmide, J. Am. Chem. Soc., 84:1994-2002, 1962.
Olson, R., et al., Orally Active Isoxazoline Glycoprotein IIb/IIIa Antagonists with Extended Duration of Action, J. Med. Chem., 42:1178-1192, 1999.
Crosby, D., et al., n-Butyl 5-Chloro-2-pyrimidoxyacetate-A Plant Growth Regulator Analog, J. Org. Chem., 25:1916-1919, Nov. 1960.

(Continued)

Primary Examiner—Deepak Rao
(74) *Attorney, Agent, or Firm*—Gibbons, Del Deo, Dolan, Griffinger, Vecchione

(57) **ABSTRACT**

The invention relates to novel sulfamides and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as endothelin receptor antagonists.

11 Claims, No Drawings

OTHER PUBLICATIONS

Morgan, E.D., Synthesis of p-Alkylphenylacetic Acid, Tetrahedron, 23:1735-1738, 1967.

Tozer, M., et al., 4-Chlorobenzyl Sulfonamide and Sulfamide Derivatives of Histamine Homologues: The Design of Potent Histamine H3 Receptor Antagonists, Bioorganic & Medicinal Chemistry Letter 9:3103-3108, 1999.

Dewynter, G., et al., Tetrahedron, 49(1):85-76, 1993.

Bennett, J. Claude, et al., Textbook of Medicine, vol. 1, 20th Edition, 1004-1010.

Rubanyi, G.M., et al., Endothelins: Molecular Biology, Biochemistry, Pharmacology, Physiology and Pathophysiology, Pharm. Reviews, 46(3), 1994.

Arai, H., et al., Cloning and expression of a cDNA encoding an endothelin receptor, Nature, 348:730-732, 1990.

Breu, V., et al., In vitro characterization of Ro 46-2005, a novel synthetic non-peptide endothelin antagonist of Eta and ETb receptors, FEBS 13244, 334(2):210-214, Nov. 1993.

Neidhart, W., et al., The Discovery of Nonpeptide Endothelin Receptor Antagonists. Progression towards Bosentan, Chimia, 50:519-524, Nov. 1996.

McMillen, M., et al., Endothelins: Polyfunctional Cytokines, J. Amer. College of Surgeons, 180:621-640, 1995.

Ogawa, Y., et al., Molecular Cloning of a Non-Isopeptide-Selective Human Endothelin Receptor, Biochem. Biophy. Research Comm., 178(1):248-255, Jul. 1991.

Ohlstein, E., et al., Endothelin-1 Modulates Vascular Smooth Muscle Structure and Vasomotion: Implications in Cardiovascular Pathology, Drug Development Research, 29:108-128, 1993.

Sakurai, T., et al., Cloning of cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor, Nature, 348:732-735, Dec. 1990.

Sumner, M., et al., Endothelin ETa and ETb receptors mediate vascular smooth muscle contraction, Br. J. Pharmacol., 107:858-860, 1992.

Yanagisawa, M., et al., A novel potent vascoconstrictor peptide produced by vascular endothelial cells, Nature, 332:411-415, Mar. 1988.

* cited by examiner

SULFAMIDES AND THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS

This application is a 371 of PCT/EP01/14182 filed Dec. 4, 2001.

The present invention relates to novel pyrimidine-sulfamides of the general formula I and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the general formula I and especially their use as endothelin receptor antagonists.

Endothelins (ET-1, ET-2, and ET-3) are 21-amino acid peptides produced and active in almost all tissues (Yanagisawa M et al.: Nature (1988) 332:411). Endothelins are potent vasoconstrictors and important mediators of cardiac, renal, endocrine and immune functions (McMillen M A et al.: J Am Coll Surg (1995) 180:621). They participate in bronchoconstriction and regulate neurotransmitter release, activation of inflammatory cells, fibrosis, cell proliferation and cell differentiation (Rubanyi G M et al.: Pharmacol Rev (1994) 46:328).

Two endothelin receptors have been cloned and characterized in mammals (ET_A, ET_B) (Arai H et al.: Nature (1990) 348:730; Sakurai T et al.: Nature (1990) 348:732). The ET_A receptor is characterized by higher affinity for ET-1 and ET-2 than for ET-3. It is predominant in vascular smooth muscle cells and mediates vasoconstricting and proliferative responses (Ohlstein E H et al.: Drug Dev Res (1993) 29:108). In contrast, the ET_B receptor has equivalent affinity for the three endothelin isopeptides and binds the linear form of endothelin, tetra-alaendothelin, and sarafotoxin S6C (Ogawa Y et al.: BBRC (1991) 178:248). This receptor is located in the vascular endothelium and smooth muscles, and is also particularly abundant in lung and brain. The ET_B receptor from endothelial cells mediates transient vasodilator responses to ET-1 and ET-3 through the release of nitric oxide and/or prostacyclin whereas the ET_B receptor from smooth muscle cells exerts vasoconstricting actions (Sumner M J et al.: Brit J Pharmacol (1992) 107:858). ET_A and ET_B receptors are highly similar in structure and belong to the superfamily of G-protein coupled receptors.

A pathophysiological role has been suggested for ET-1 in view of its increased plasma and tissue levels in several disease states such as hypertension, pulmonary hypertension, sepsis, atherosclerosis, acute myocardial infarction, congestive heart failure, renal failure, migraine and asthma. As a consequence, endothelin receptor antagonists have been studied extensively as potential therapeutic agents. Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in various diseases such as cerebral vasospasm following subarachnoid hemorrhage, heart failure, pulmonary and systemic hypertension, neurogenic inflammation, renal failure and myocardial infarction.

Today, only one endothelin receptor antagonist (Tracleer™) is marketed and several are in clinical trials. However, some of these molecules possess a number of weaknesses such as complex synthesis, low solubility, high molecular weight, poor pharmacokinetics, or safety problems (e.g. liver enzyme increases). Furthermore, the contribution of differing ET_A/ET_B receptor blockade to the clinical outcome is not known. Thus, tailoring of the physicochemical and pharmacokinetic properties and the selectivity profile of each antagonist for a given clinical indication is mandatory. So far, no endothelin receptor antagonists with a pyrimidine core structure containing a sulfamide unit, have been reported [2, 3, 5, 6, 8]. We have discovered a new class of substituted pyrimidines of the structure below and found that they allow the specific tailoring described above and in addition compounds exhibiting mixed as well as ET_A-selective binding profiles have been identified.

The inhibitory activity of the compounds of general formula I on endothelin receptors can be demonstrated using the test procedures described hereinafter:

For the Evaluation of the Potency and Efficacy of the Compounds of the General Formula I the Following Tests were used:

1) Inhibition of Endothelin Binding to Membranes from CHO Cells Carrying Human ET Receptors:

For competition binding studies, membranes of CHO cells expressing human recombinant ET_A or ET_B receptors were used. Microsomal membranes from recombinant CHO cells were prepared and the binding assay made as previously described (Breu V., et al, FEBS Lett 1993; 334:210).

The assay was performed in 200 uL 50 mM Tris/HCl buffer, pH 7.4, including 25 mM $MnCl_2$, 1 mM EDTA and 0.5% (w/v) BSA in polypropylene microtiter plates. Membranes containing 0.5 ug protein were incubated for 2 h at 20° C. with 8 pM [^{125}I]ET-1 (4000 cpm) and increasing concentrations of unlabelled antagonists. Maximum and minimum binding were estimated in samples without and with 100 nM ET-1, respectively. After 2 h, the membranes were filtered on filterplates containing GF/C filters (Unifilterplates from Canberra Packard S.A. Zürich, Switzerland). To each well, 50 uL of scintillation cocktail was added (MicroScint 20, Canberra Packard S.A. Zürich, Switzerland) and the filter plates counted in a microplate counter (TopCount, Canberra Packard S.A. Zürich, Switzerland).

All the test compounds were dissolved, diluted and added in DMSO. The assay was run in the presence of 2.5% DMSO which was found not to interfere significantly with the binding. IC_{50} was calculated as the concentration of antagonist inhibiting 50% of the specific binding of ET-1. For reference compounds, the following IC_{50} values were found: ET_A cells: 0.075 nM (n=8) for ET-1 and 118 nM (n=8) for ET-3; ET_B cells: 0.067 nM (n=8) for ET-1 and 0.092 nM (n=3) for ET-3.

The IC_{50} values obtained with compounds of general formula I are given in Table 1.

TABLE 1

	IC_{50} [nM]	
Compound of Example	ET_A	ET_B
Example 1	721	8429
Example 2	2190	8743
Example 3	1384	744
Example 4	96	680
Example 5	28	1280
Example 6	286	7240
Example 7	1237	9467
Example 8	1160	>10000
Example 9	3629	>10000
Example 10	2866	193
Example 12	59	>10000
Example 14	5.6	1033
Example 15	18.5	2161
Example 16	45	8452
Example 18	8.5	3333
Example 19	25	3414
Example 20	4.9	1723
Example 21	7	1001
Example 22	12	434
Example 23	3.6	1585

TABLE 1-continued

Compound of Example	IC_{50} [nM] ET_A	IC_{50} [nM] ET_B
Example 24	2.2	2496
Example 26	54	>10000
Example 29	13.5	4230
Example 32	3.5	864
Example 33	3.7	609
Example 34	23	3267
Example 37	16	822
Example 38	14.5	290
Example 39	32.7	524
Example 41	3.2	41.6
Example 42	3.5	146
Example 43	6.8	214
Example 48	1.46	46.6
Example 49	0.82	25.4
Example 50	0.87	7.5
Example 51	13.4	306
Example 55	5.2	80
Example 56	6.9	164
Example 57	4.9	35.8
Example 59	5.6	124
Example 60	3.4	232
Example 61	1.6	200
Example 66	11	487
Example 71	23.6	635
Example 73	1.9	567
Example 74	1.8	164
Example 75	14	895
Example 80	10	>1000
Example 81	3.6	274
Example 84	37	574
Example 88	16	1251
Example 89	19	621
Example 90	7.4	433
Example 91	2.5	79
Example 96	6.3	585
Example 97	1.55	92
Example 98	2.1	159
Example 100	0.76	283
Example 101	1.24	335
Example 102	0.46	65
Example 104	0.88	601
Example 105	0.69	203
Example 107	0.25	96
Example 108	0.28	56
Example 109	1.94	>1000
Example 110	2.3	>1000
Example 111	12.3	3750
Example 112	0.52	257
Example 113	4.26	581
Example 114	8.3	>1000
Example 115	2.2	>1000
Example 116	1.3	567
Example 117	0.45	518
Example 118	0.34	611
Example 119	4.2	>1000
Example 123	2.9	124
Example 124	7.3	102
Example 127	7.3	87
Example 130	3.7	347
Example 131	3.2	233
Example 133	1.7	212
Example 134	2.4	187
Example 137	2.7	173
Example 138	0.9	40
Example 142	2.6	108
Example 143	3.1	35
Example 145	1.64	>1000
Example 146	5	514
Example 147	1.2	408
Example 149	15	1315
Example 151	0.77	57
Example 152	1.1	79
Example 155	5.8	173
Example 156	18	409
Example 157	42.2	954

TABLE 1-continued

Compound of Example	IC_{50} [nM] ET_A	IC_{50} [nM] ET_B
Example 158	10	80
Example 160	11	3221
Example 161	6.2	>1000
Example 163	0.44	80
Example 164	1	81
Example 166	1	3
Example 167	5.2	6.4
Example 168	2.7	1.6
Example 170	1.7	42
Example 171	11	61
Example 172	3	16
Example 174	3.7	93
Example 175	22	62
Example 176	2.5	22
Example 181	14.3	224
Example 182	29	1867
Example 184	29.5	3777
Example 187	9.8	532
Example 188	11	290
Example 193	3.6	>1000
Example 194	9.5	>1000
Example 196	4.4	>1000
Example 197	1.16	418
Example 198	38.4	667
Example 199	12	205
Example 200	23	310
Example 201	133	682
Example 202	9.6	351
Example 204	390	1047
Example 205	135	623
Example 206	1.03	209
Example 207	17	>1000
Example 208	17	342
Example 209	733	>1000
Example 210	23	936
Example 211	290	722
Example 212	3.1	>1000
Example 213	1.32	347
Example 214	0.76	241

2) Inhibition of Endothelin-induced Contractions on Isolated Rat Aortic Rings (ET_A Receptors) and Rat Tracheal Rings (ET_B Receptors):

The functional inhibitory potency of the endothelin antagonists was assessed by their inhibition of the contraction induced by endothelin-1 on rat aortic rings (ET_A receptors) and of the contraction induced by sarafotoxin S6c on rat tracheal rings (ET_B receptors). Adult Wistar rats were anesthetized and exsanguinated. The thoracic aorta or trachea were excised, dissected and cut in 3–5 mm rings. The endothelium/epithelium was removed by gentle rubbing of the intimal surface. Each ring was suspended in a 10 ml isolated organ bath filled with Krebs-Henseleit solution (in mM; NaCl 115, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5, glucose 10) kept at 37° C. and gassed with 95% O_2 and 5% CO_2. The rings were connected to force transducers and isometric tension was recorded (EMKA Technologies SA, Paris, France). The rings were stretched to a resting tension of 3 g (aorta) or 2 g (trachea). Cumulative doses of ET-1 (aorta) or sarafotoxin S6c (trachea) were added after a 10 min incubation with the test compound or its vehicle. The functional inhibitory potency of the test compound was assessed by calculating the concentration ratio, i.e. the shift to the right of the EC_{50} induced by different concentrations of test compound. EC_{50} is the concentration of endothelin needed to get a half-maximal con-

traction, pA_2 is the negative logarithm of the antagonist concentration which induces a two-fold shift in the EC_{50} value.

The pA_2 values obtained with compounds of formula I are given in Table 2.

TABLE 2

Compound of Example	pA_2 value ET_A	ET_B
Example 5	6.65	
Example 14	8.4	5.63
Example 18	8.15	<5
Example 20	7.21	
Example 32	8.75	
Example 37	7.83	
Example 41	8.37	
Example 51	6.55	
Example 100	8.44	
Example 102	8.40	6.76
Example 119	7.38	
Example 133	7.72	
Example 161	6.29	
Example 203	7.69	5.84

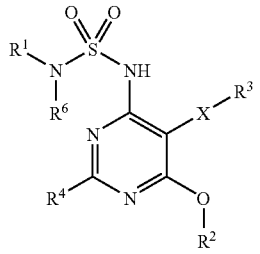
Because of their ability to inhibit the endothelin binding, the described compounds can be used for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome and portal hypertension. They can also be used in the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia as well as other diseases, presently known to be related to endothelin.

The compounds can be administered orally, rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol. Examples of applications are capsules, tablets, orally administered suspensions or solutions, suppositories, injections, eye-drops, ointments or aerosols/nebulizers.

Preferred applications are intravenous, intra-muscular, or oral administrations as well as eye drops. The dosage used depends upon the type of the specific active ingredient, the age and the requirements of the patient and the kind of application. Generally, dosages of 0.1–50 mg/kg body weight per day are considered. The preparations with compounds can contain inert or as well pharmacodynamically active excipients. Tablets or granules, for example, could contain a number of binding agents, filling excipients, carrier substances or diluents.

The present invention relates to pyrimidine-sulfamides of the general formula I,

General Formula I



wherein

R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; hydrogen or may form a heterocyclyl- or cycloalkyl-ring together with R^6;

R^2 represents $—CH_3$; $—(CH_2)_n—Y—R^a$; $—(CH_2)_m—C{\equiv}C—(CH_2)_p\text{-}Z\text{-}R^a$; $—(CH_2)_k—C(R^b){=}CR^cR^d$; $—CH_2$-tetrahydrofuran-2-yl;

R^3 represents aryl; heteroaryl;

R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N-(lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; heteroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy; heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocydyl-lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; cycloalkyl-sulfinyl;

R^6 represents hydrogen; lower alkyl; or may form a heterocyclyl- or cycloalkyl-ring together with R^1;

X represents oxygen; sulfur; $—CH_2—$ or a bond;

Y represents a bond, —O—; —NH—; $—NH—SO_2—$; $—NH—SO_2NH—$; O—CO—; —CO—O—; —O—CO—NH—; —NH—CO—O—; —NH—CO—NH—

Z represents oxygen or a bond;

k represents the whole numbers 1, 2, 3, 4, 5 or 6;

n represents the whole numbers 2, 3, 4, 5 or 6;

m represents the whole numbers 1, 2, 3, 4 or 5;

p represents the whole numbers 0 (zero), 1, 2 or 3 and if p represents the whole number 0 (zero), Z cannot represent oxygen;

R^a represents aryl; heteroaryl; lower alkyl; cycloalkyl; hydrogen;

R^b and R^c independently represent hydrogen or lower alkyl;

R^d represents represents hydrogen; lower alkyl; aryl; heteroaryl; and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure

diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

In the definitions of the general formula I—if not otherwise stated—the expression lower means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms. Examples of lower alkyl and lower alkoxy groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, hexyl, heptyl, methoxy, ethoxy, propoxy, butoxy, iso-butoxy, sec.-butoxy and tert.-butoxy. Lower alkylendioxy-groups are preferably methylen-dioxy and ethylen-dioxy groups. Examples of lower alkanoyl-groups are acetyl, propanoyl and butanoyl. Lower alkenylen means e.g. vinylen, propenylen and butenylen. Lower alkenyl and lower alkynyl means groups like ethenyl, propenyl, butenyl, 2-methyl-propenyl, and ethinyl, propinyl, butinyl, pentinyl, 2-methyl-pentinyl. Lower alkenyloxy means allyloxy, vinyloxy and propenyloxy. The expression cycloalkyl means a saturated cyclic hydrocarbon ring with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which may be substituted with lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, and lower alkoxy-lower alkyl groups. The expression heterocyclyl means saturated or unsaturated (but not aromatic), four, five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings may be adequatly substituted with lower alkyl, lower alkoxy, e.g. piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, dihydroimidazolyl, dihydropyrazolyl, pyrazolidinyl and substituted derivatives of such rings with substituents as outlined above. The expression heteroaryl means six-membered aromatic rings containing one to four nitrogen atoms, benzo-fused six-membered aromatic rings containing one to three nitrogen atoms, five-membered aromatic rings containing one oxygen or one nitrogen or one sulfur atom, benzo-fused five-membered aromatic rings containing one oxygen or one nitrogen or one sulfur atom, five membered aromatic rings containig an oxygen and nitrogen atom and benzo fused derivatives thereof, five membered aromatic rings containing a sulfur and a nitrogen atom and benzo fused derivatives thereof, five-membered aromatic rings containing two nitrogen atoms and benzo fused derivatives thereof, five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring; e.g. furanyl, thienyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, oxazolyl, isoxazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, 5-thioxo-1,2,4-oxadiazolyl, 2-oxo-1,2,3,5-oxathiadiazolyl, whereby such rings may be substituted with lower alkyl, lower alkenyl, amino, amino-lower alkyl, halogen, hydroxy, lower alkoxy, trifluoromethoxy, trifluoromethyl, carboxyl, carboxamidyl, thioamidyl, amidinyl, lower alkoxy-carbonyl, cyano, hydroxy-lower alkyl, lower alkyl-oxy-lower alkyl or another heteroaryl- or heterocyclyl-ring. The expression aryl represents unsubstituted as well as mono-, di- or tri-substituted aromatic rings with 6 to 10 carbon atoms like phenyl or naphthyl rings which may be substituted with aryl, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkenyloxy, lower alkynyl-lower alkyl-oxy, lower alkenylen, lower alkylenoxy or lower alkylendioxy forming with the phenyl ring a five- or six-membered ring, hydroxy-lower alkyl, hydroxy-lower alkenyl, hydroxy-lower alkyl-lower alkynyl, lower alkyloxy-lower alkyl, lower alkyloxy-lower alkyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyl, hydroxy-cycloalkyl, heterocyclyl, heteroaryl.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p-toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula I might have one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and also in the meso-form. The present invention encompasses all these forms. Mixtures may be separated in a manner known per se, i.e. by column chromatography, thin lay r chromatography, HPLC or crystallization.

Because of their ability to inhibit the endothelin binding, the described compounds of the general formula I and their pharmaceutically acceptable salts may be used for treatment of diseases which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, portal hypertension and pulmonary hypertension. They can also be used for the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia as well as other diseases presently known to be related to endothelin.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered intramuscularly, parenterally or intraveneously, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols may be used. For the preparation of solutions and sirups e.g. water, polyols, saccharose, glucose can be used. Injectables can be prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin or liposomes. Suppositories may be prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols.

The compositions may contain in addition preservatives, stability improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer or anti-oxidants.

The compounds of general formula I may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol and the like; vasodilators like hydralazine, minoxidil, diazoxide or flosequinan; calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil or nifedipine; ACE-inhibitors like cilazapril, captopril, enalapril, lisinopril and the like; potassium activators like pinacidil; angiotensin II receptor antagonists like losartan, valsartan, irbesartan and the like; diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone or chlortalidone; sympatholitics like methyidopa, clonidine, guanabenz or reserpine and other therapeutics which serve to treat high blood pressure or any cardiac disorders.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual children should receive lower doses which are adapted to body weight and age.

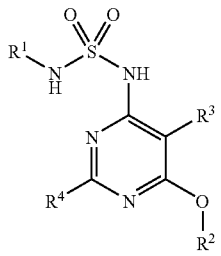
Preferred compounds are compounds of general formula I wherein R^3 represents phenyl or mono-substituted phenyl substituted with lower alkyloxy, especially methoxy and X represents oxygen and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

A second group of preferred compounds of general formula I are those wherein R^3 represents phenyl or mono-substituted phenyl substituted with lower alkoxy, especially methoxy, X represents oxygen and R^2 represents $—(CH_2)_n—Y—R^a$ and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

A third group of preferred compounds of general formula I are those wherein R^3 represents phenyl or mono-substituted phenyl substituted with lower alkoxy, especially methoxy, X represents oxygen and R^2 represents $—(CH_2)_2—O—R^a$, with R^a being heteroaryl and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

Another group of preferred compounds are compounds of formula II

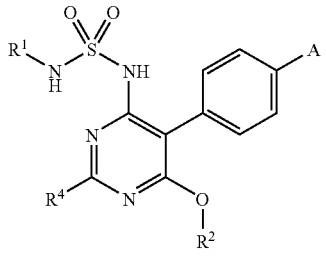
Formula II



wherein R^1, R^2, R^3 and R^4 are as defined in general formula I above and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula II.

Also preferred are compounds of formula III

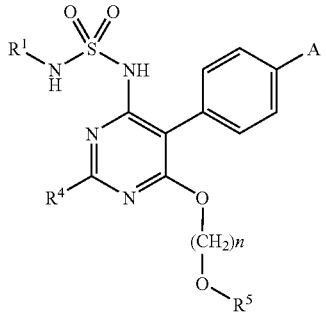
Formula III



wherein R^1, R^2 and R^4 are as defined in general formula I above and A represents is hydrogen, methyl, ethyl, chlorine, bromine, fluorine, trifluoromethyl or methoxy and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereom ric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula III.

Also preferred are compounds of formula IV

Formula IV

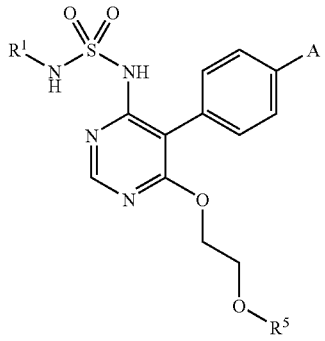


wherein R^1, R^4 and n are as defined in general formula I above and A is as defined in formula III above and R^5 represents hydrogen, lower alkyl, aryl, heteroaryl and cycloalkyl, and optically pure enantiomers or diastereomers,

mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula IV.

Another especially preferred group of compounds are compounds of formula V

Formula V



wherein R^1 is as defined in general formula I above, A is as defined in formula III above and R^5 represents hydrogen, lower alkyl, aryl, heteroaryl and cycloalkyl, and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula IV.

Especially preferred compounds among the group of compounds of formula V are those wherein R^5 represents heteroaryl and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

Preferred compounds are:

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(4-methoxy-benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']biprimidinyl-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Benzylsulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid-[5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-Bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-2-pyridin-4-yl-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-2-pyridin-4-yl-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

More preferred compounds are:

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

2-Pyridylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

2-Thienylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

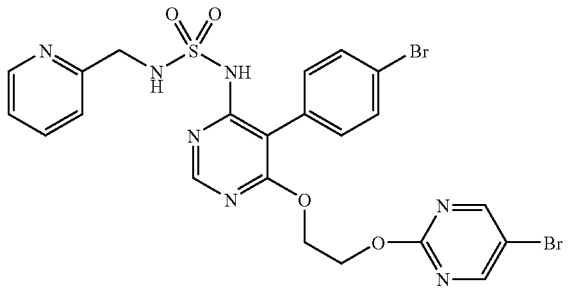
Most preferred compounds are:

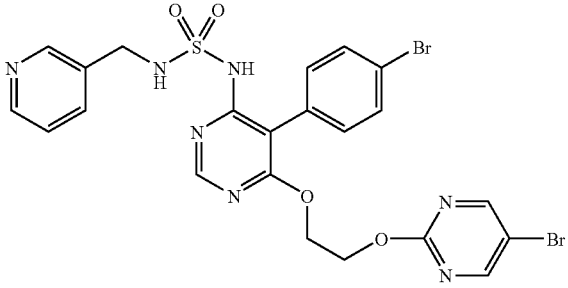
Benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

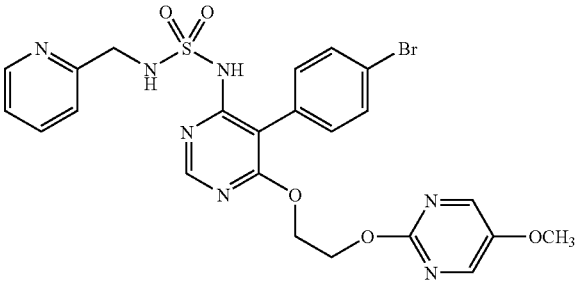
and pharmaceutically acceptable salts thereof.

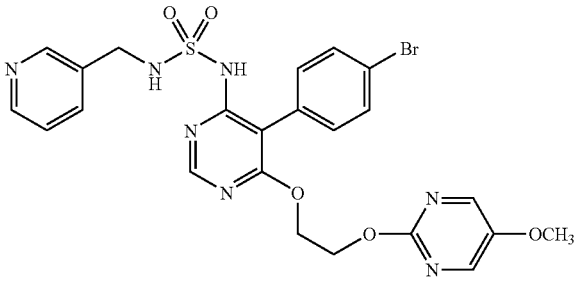
Another group of preferred compounds is depicted below:

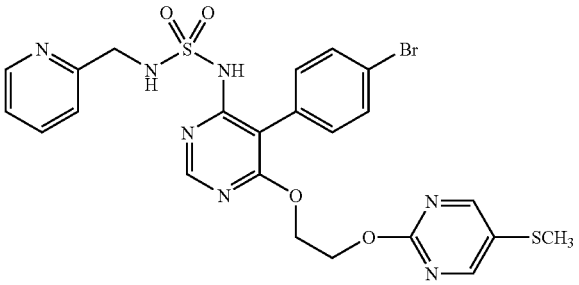


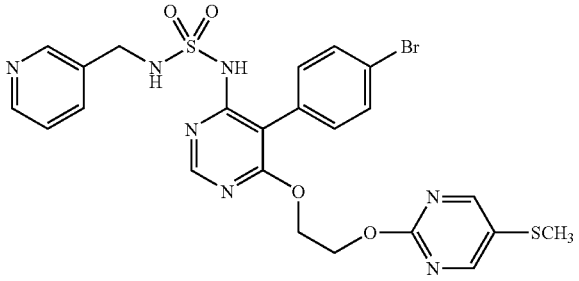


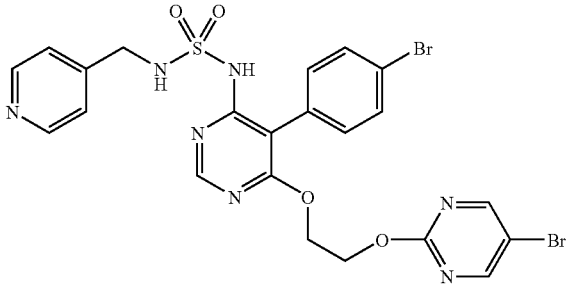
-continued

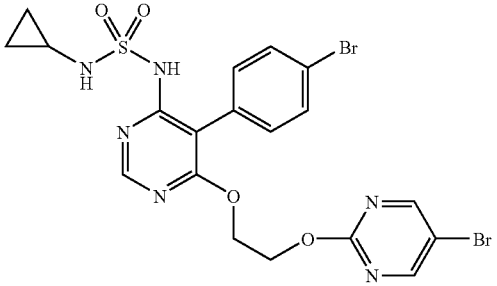




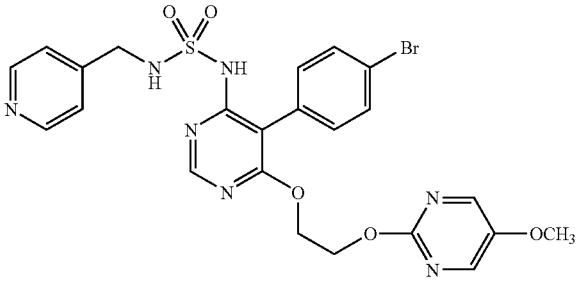


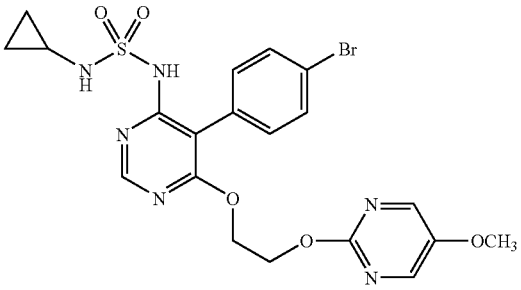


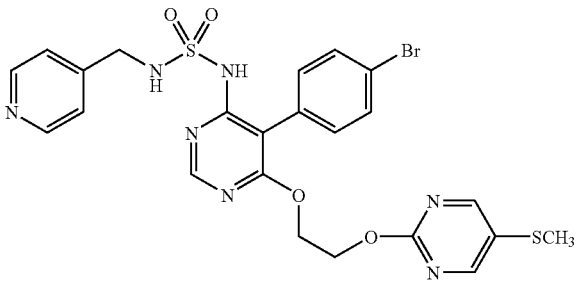


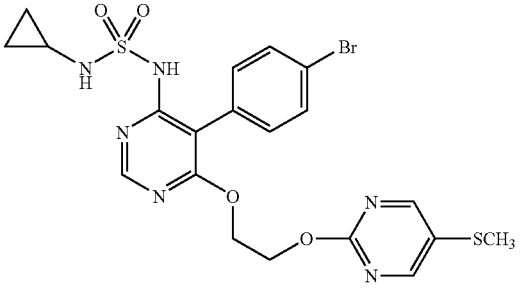


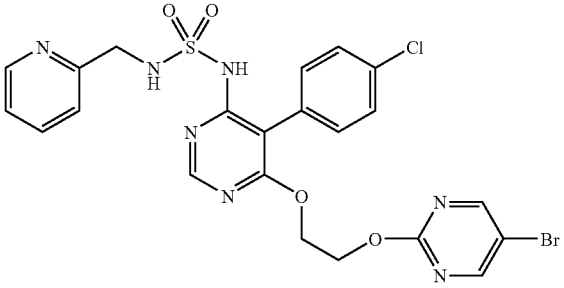
-continued



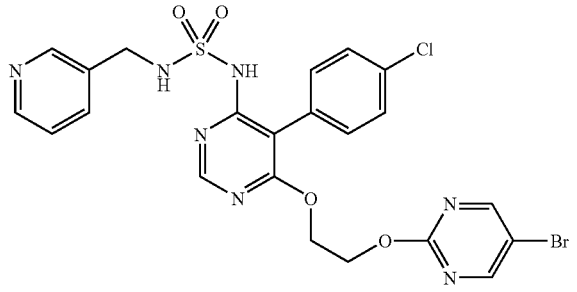


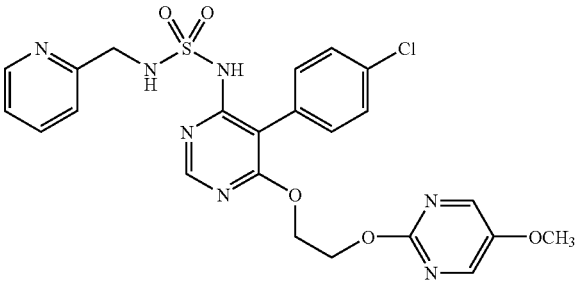


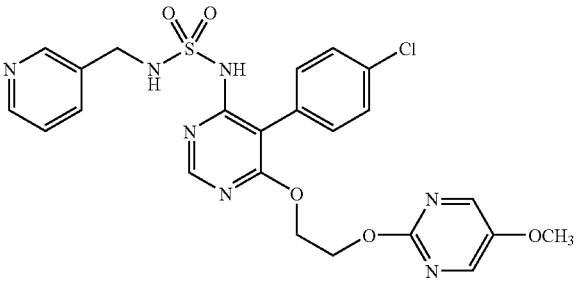


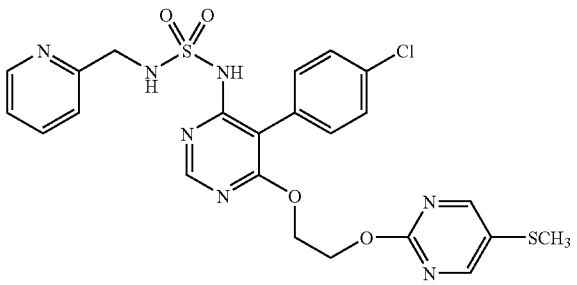


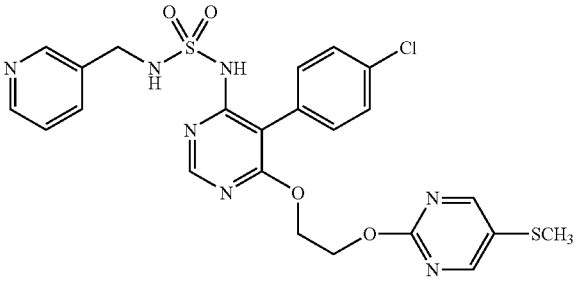
-continued



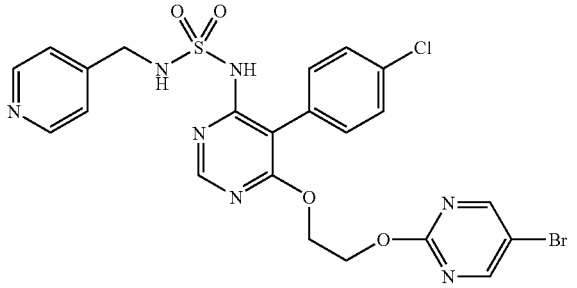


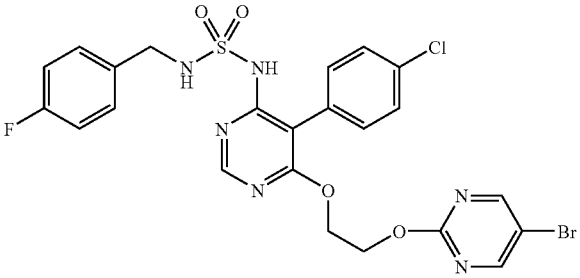


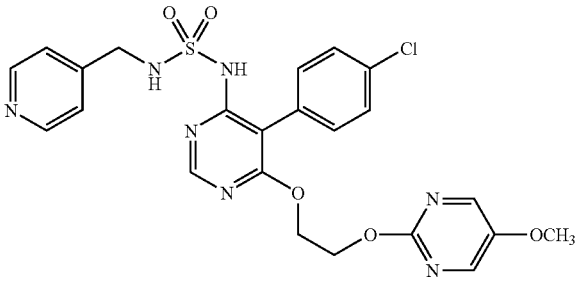


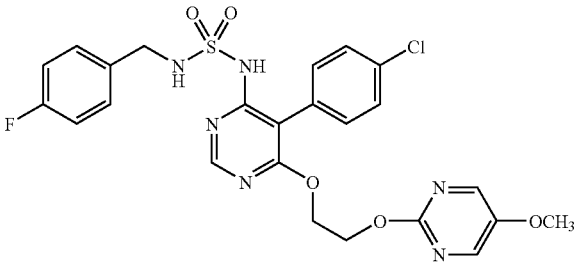


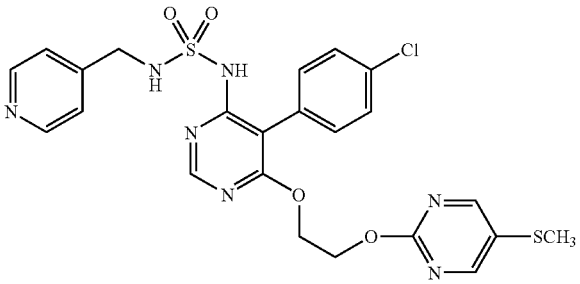
-continued

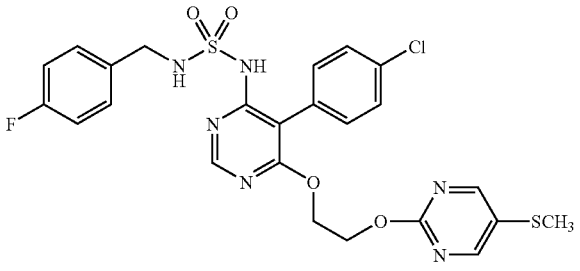




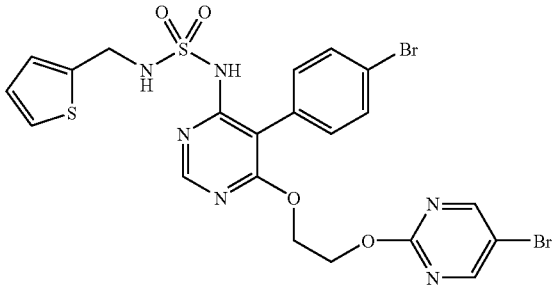


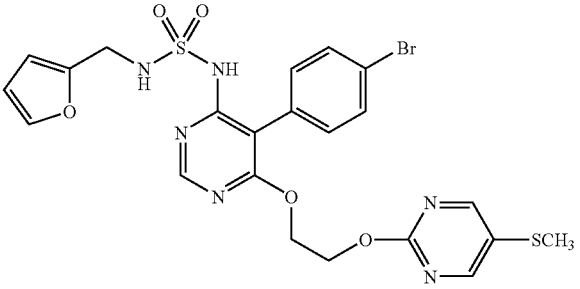


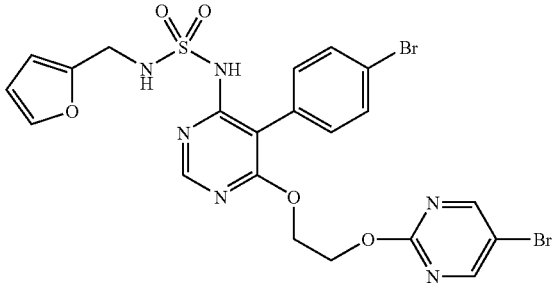


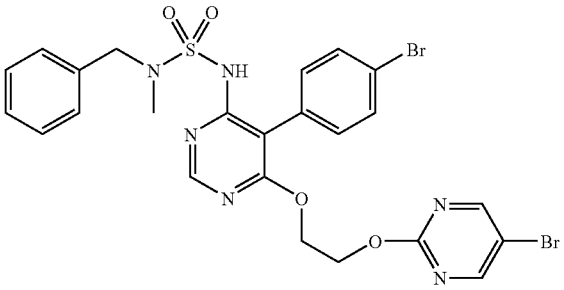


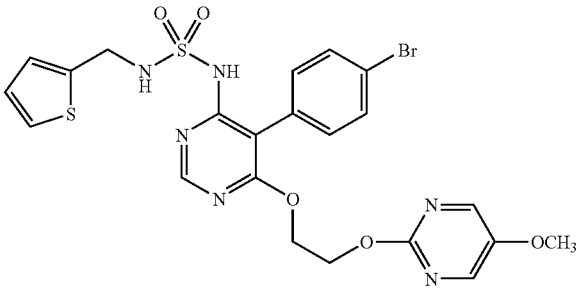
-continued

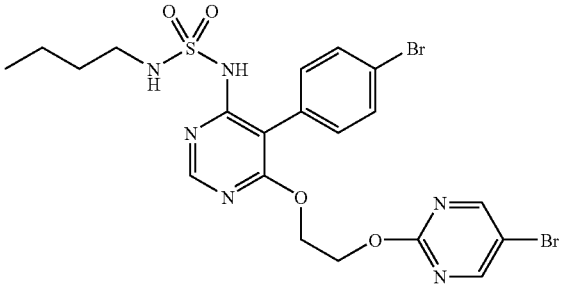


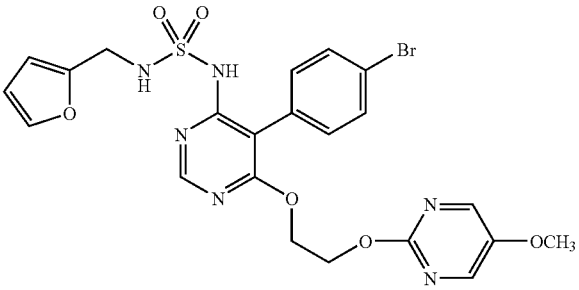


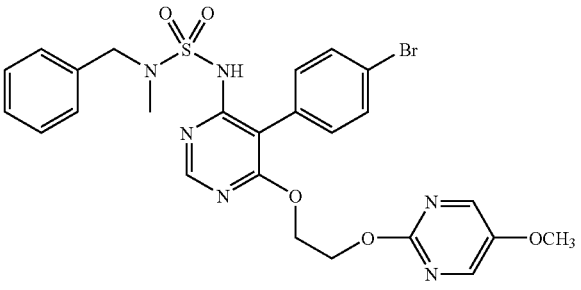


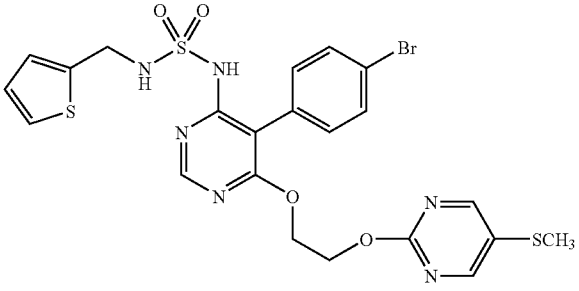


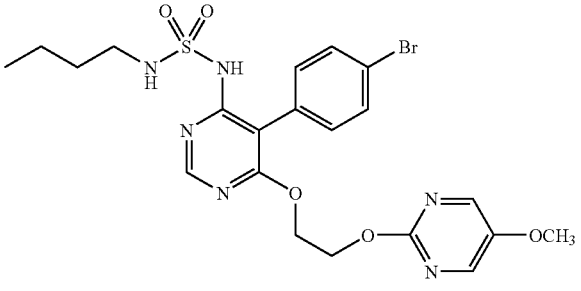




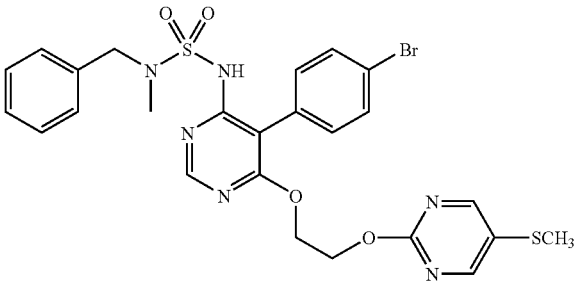


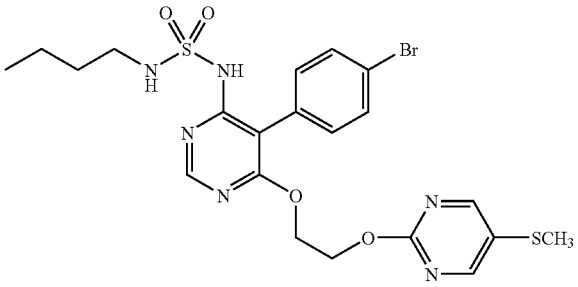


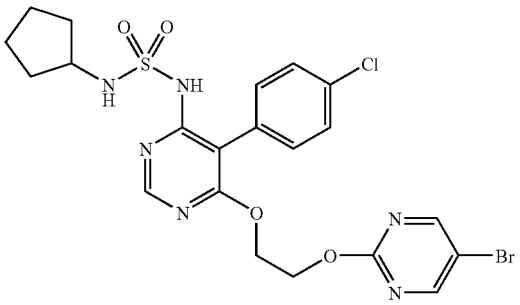


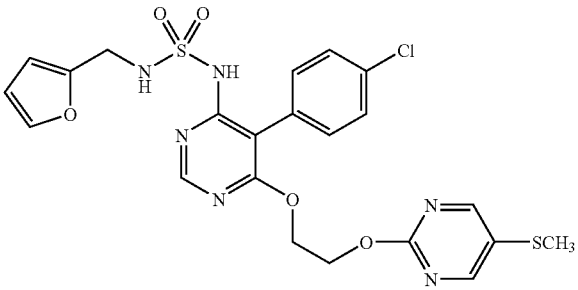


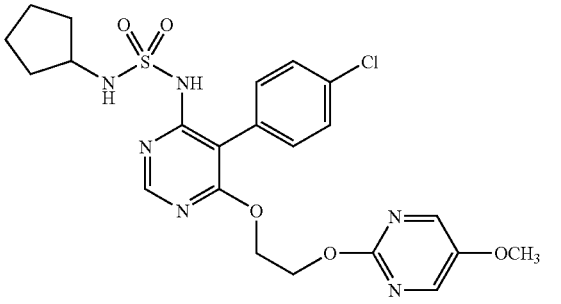
-continued



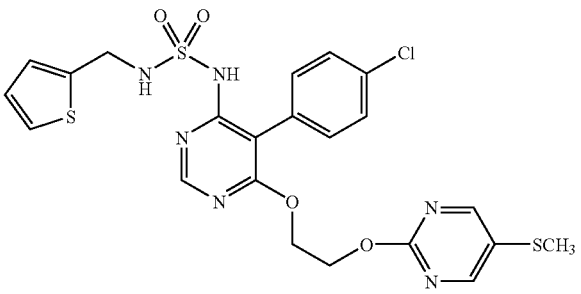


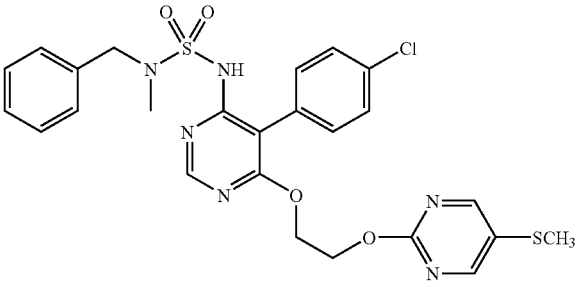


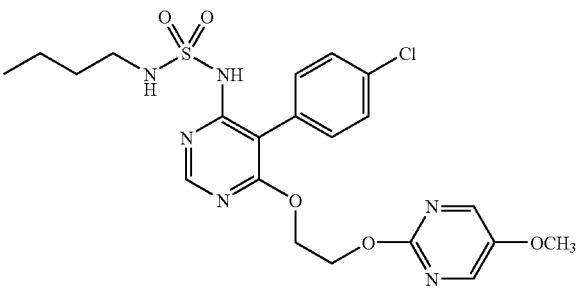


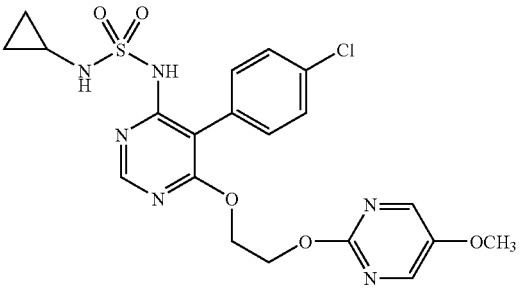


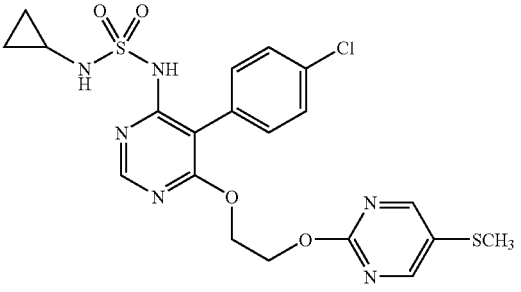
-continued



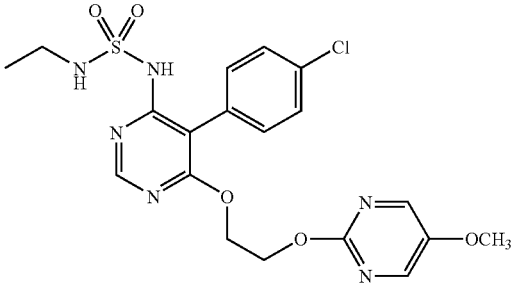


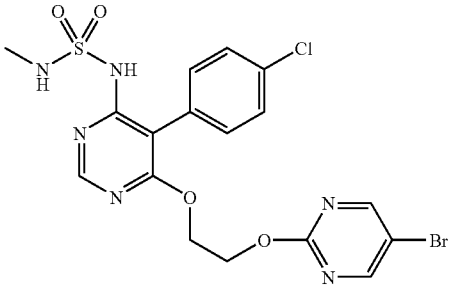


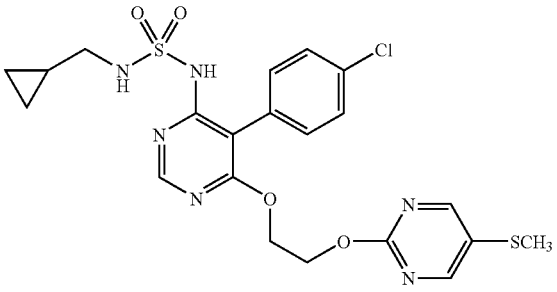


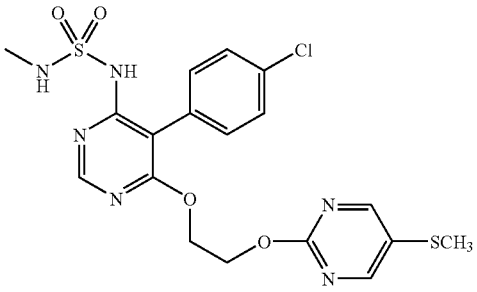


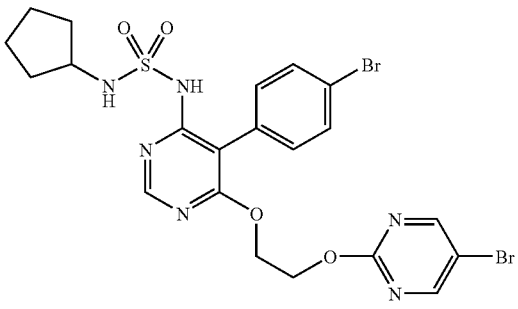
-continued



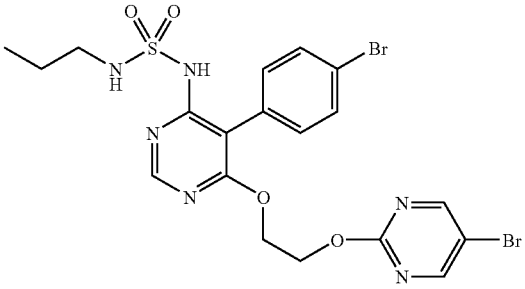


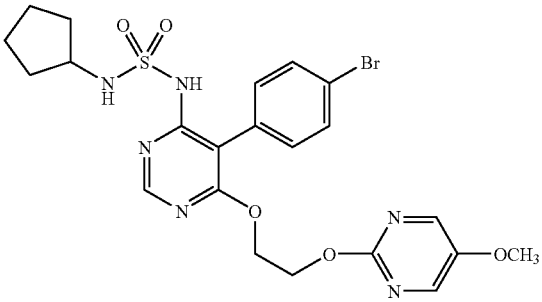


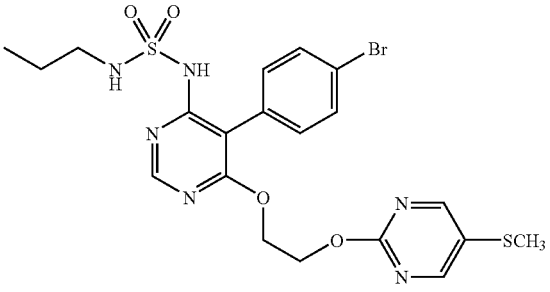


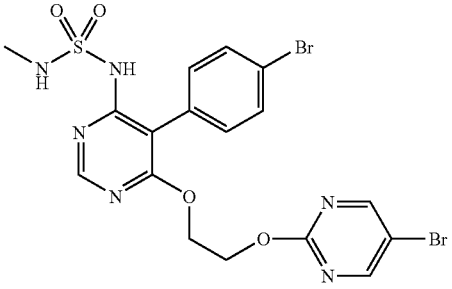


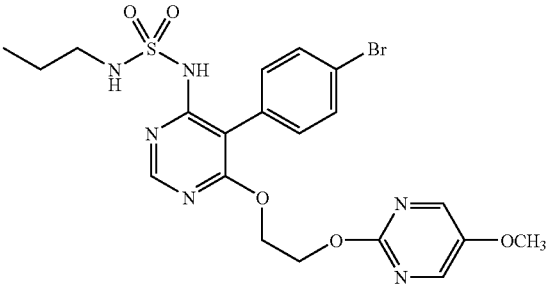
-continued



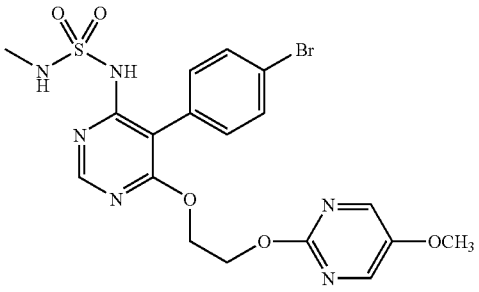


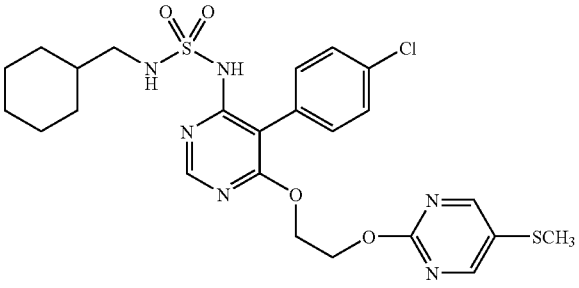


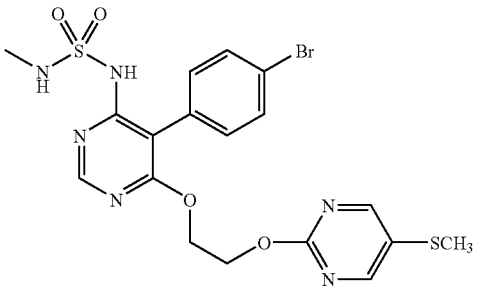


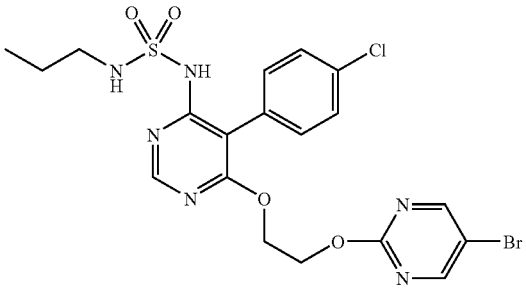


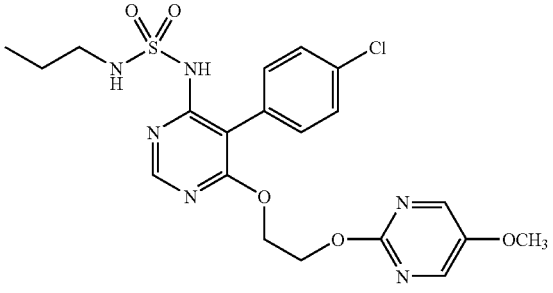
-continued



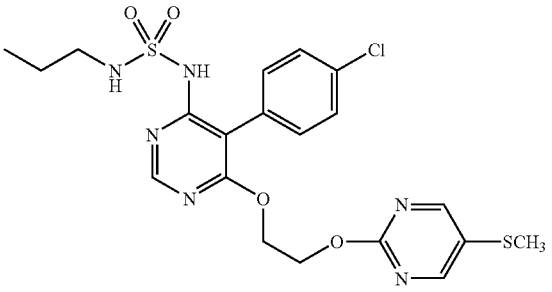








-continued

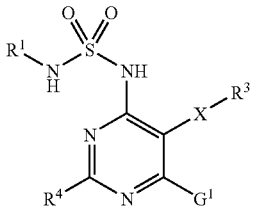


Compounds of the general formula I of the present invention can be prepared according to the general sequence of reactions outlined below. For simplicity and clarity reasons sometimes only parts of the synthetic possibilities which lead to compounds of general formula I are described. The literature references given in brackets [ ] are set forth at the end of this paragraph.

Possibility A:

The desired compounds of general formula I can be prepared by reacting a compound of the formula 1:

Formula 1



wherein G^1 is a reactive residue, preferentially a chloro atom, and the other symbols are as defined in general formula I above, with a compound of the formula 2:

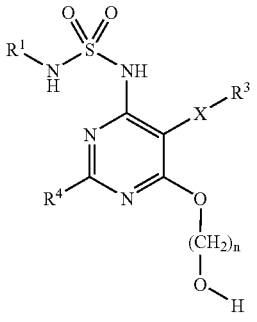
R^2—OH Formula 2

wherein the symbols are the same as defined in general formula I above, or a salt thereof.

Possibility B:

The compounds of general formula I may also be prepared by reacting a compound of formula 3:

Formula 3



wherein the symbols are the same as defined in general formula I above, or a salt thereof, with a compound of the formula 4:

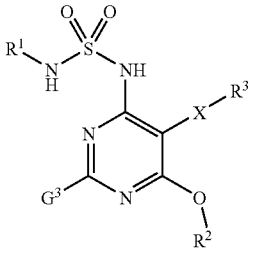
G^2-R^5 Formula 4

wherein G^2 is a reactive residue, preferentially a halogen atom, and R^5 is the same as defined in formula IV above.

Possibility C:

The compounds of general formula I may also be prepared by reacting a compound of the formula 5:

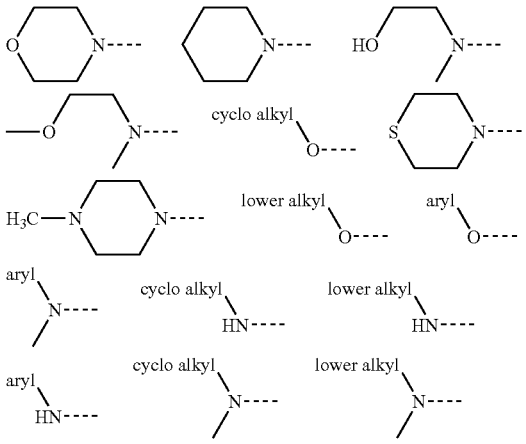
Formula 5



Wherein G^3 is a lower alkylsulfonyl group or a phenylsulfonylgroup or a halogen atom, and the other symbols are the same as described in general formula I above, or a salt thereof, with a compound of the formula 6:

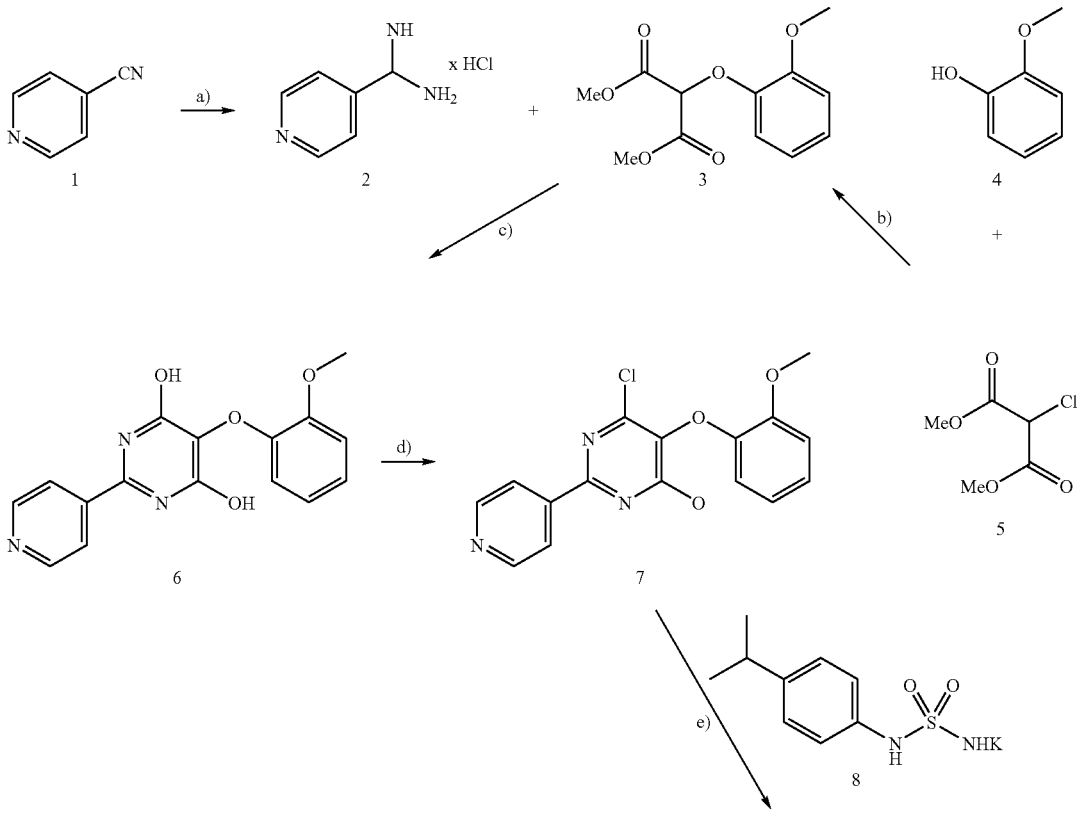
$R^{4'}$—H Formula 6

wherein $R^{4'}$ represents:

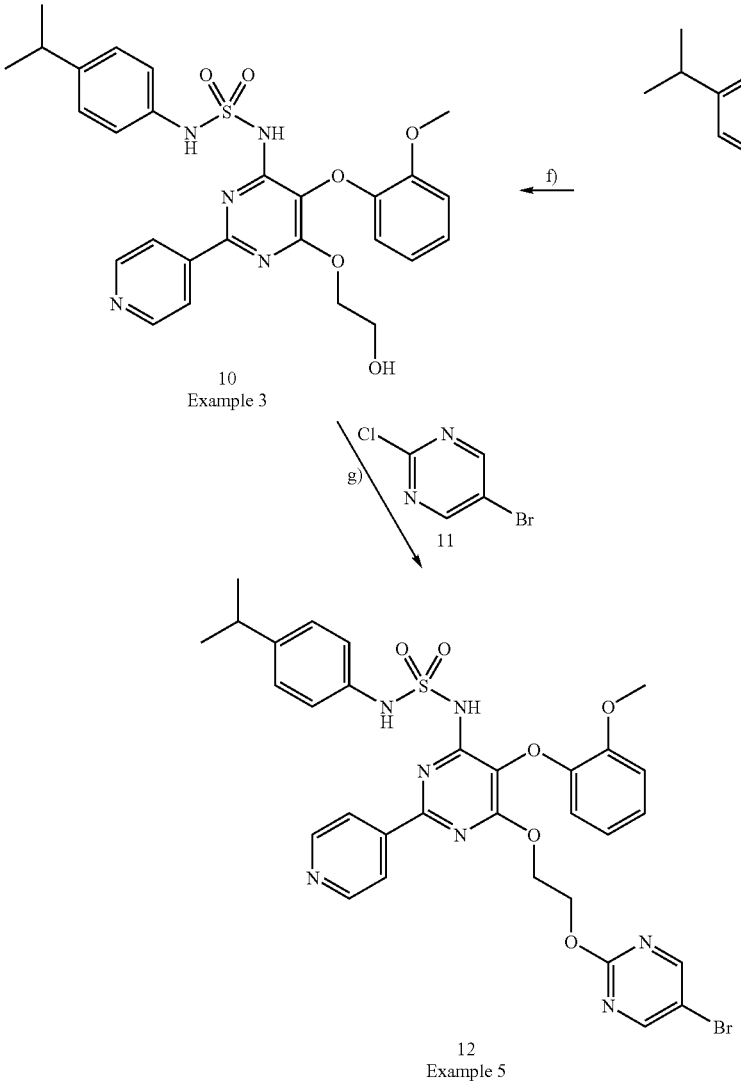


For possibilities A to C see also [5]

Scheme 1: Schematically exemplified synthesis of Example 3 and Exampl 5:



-continued



10
Example 3

9

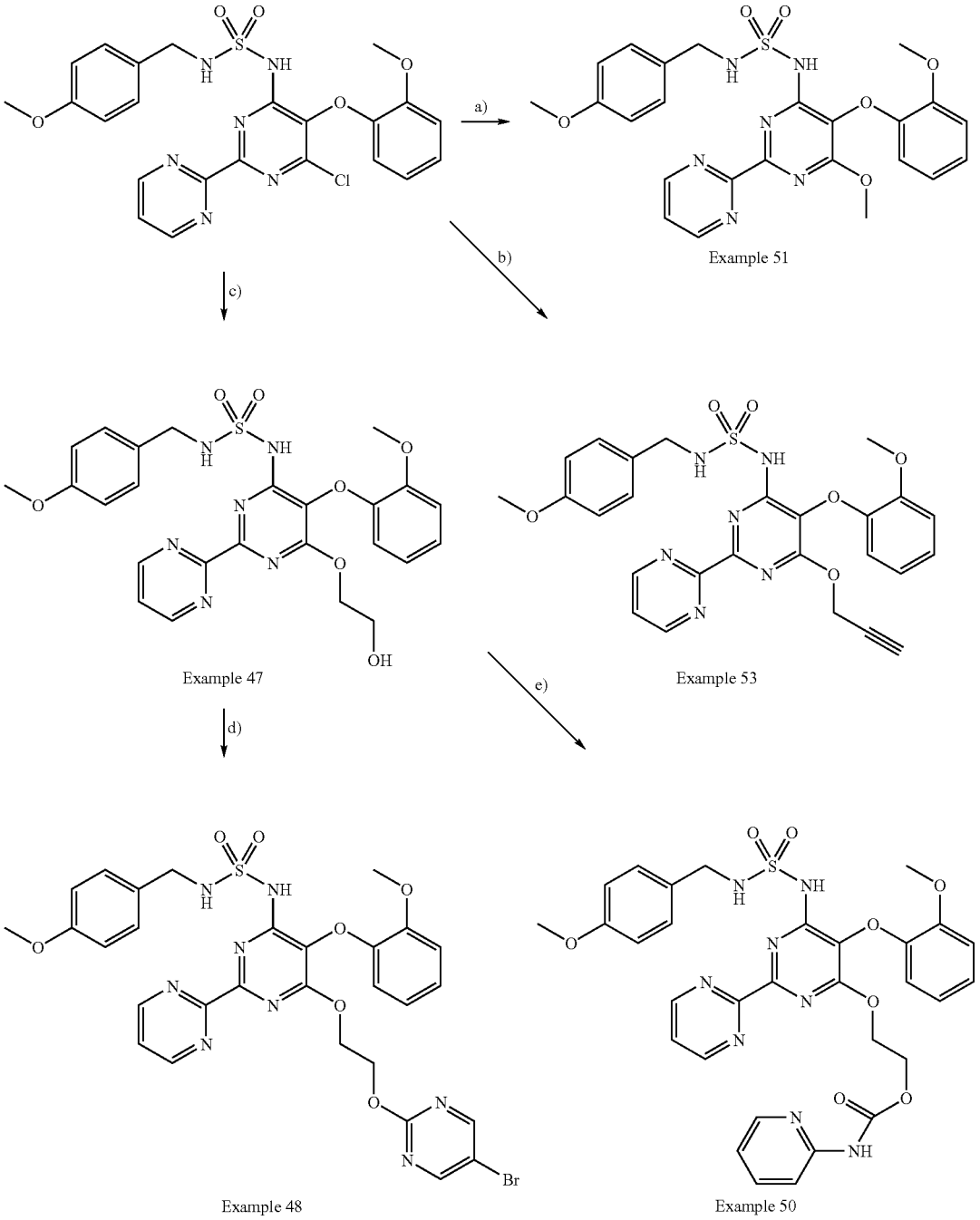
11

12
Example 5

a) NaOMe, MeOH then NH_4Cl; b) K_2CO_3, acetone, rflx; c) NaOMe, MeOH; d) $POCl_3$, N,N-dimethylaniline, 70–130° C.; e) 8, DMSO; f) Na, ethyleneglycol; 80–100° C.; g) 11, THF, NaH, rt–70° C.

In Scheme 1 the synthetic procedure to prepare compounds of the general formula I is depicted by the description of the synthesis of Example 3 and Example 5. The other examples given in this document can be prepared via the same synthetic pathway, adapting the substituents and reaction conditions. The literature references given in [ ] are set forth at the end of this paragraph. The amidines 2 were synthesized applying standard methodology [1] by reaction of the appropriate nitrile 1 with sodium methylate in methanol followed by addition of ammonium chloride. The 2-substituted malonic esters 3 were prepared according to published procedures [2] by reacting dimethylchloromalonate (5) with the appropriate alcohol 4 in acetone and potassium carbonate as base. The compounds 3 were dissolved in methanol, sodium methylate was added, and stirring was continued for about 30 min followed by the addition of an amidine derivative 2. Stirring at ambient temperature was continued for another 8 h. After acidic work up the 4,6-dihydroxypyrimidines 6 could be isolated in yields of 70 to 90% [2]. Compounds 6 or the tautomeric form thereof were transformed into the dichloro derivatives 7 with phosphorus oxychloride in the presence of N,N-dimethylaniline at elevated temperatures (60–120° C.) in yields of 40 to 75% [3]. The dichlorides 7 were reacted with an excess of the appropriate sulfamide potassium salt 8 (prepared as described in Scheme 3) in DMSO at r.t. or 40 to 60° C. to give the monochloro-pyrimidines 9 in yields of 70 to 90% either after recrystallization from ethyl acetate/diethylether or chromatography through silica gel with ethyl acetate/heptane. The pyrimidine derivatives 9 are then reacted with ethylene glycol (or another 1-ω-diol, or a mono alcohol) in the presence of a base like potassium tert.-butylate, sodium hydride or sodium at 80–110° C. for 4 to 16 h to give compounds 10 as the first claimed compounds in yields of 50 to 70%, which can be further transformed to compounds 12 by reaction with 2-chloro-5-bromopyrimidine (11) (or another suitable pyrimidine or pyridine derivative) in THF/DMF ~5/1 at either r.t. or at 50–70° C. in yields of 50–80%.

Scheme 2: Schematically exemplified synthesis of Examples 47, 48, 50, 51, 53:

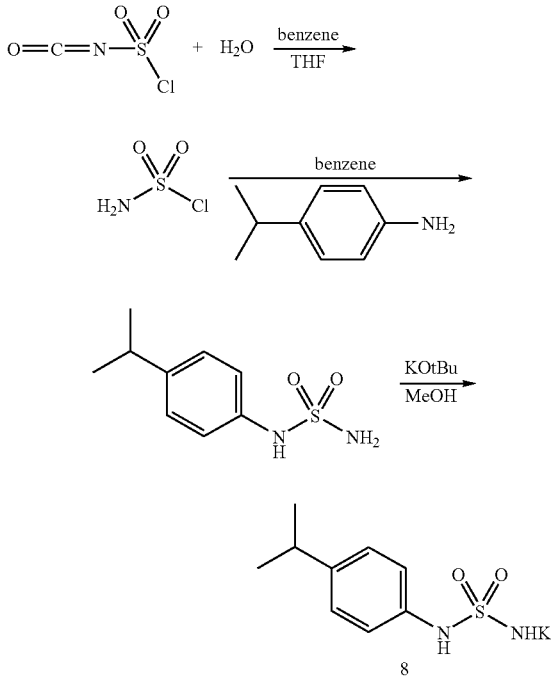


a) NaOMe, MeOH, rflx;
b) Propargyl alcohol, NaH, THF, rflx;
c) Ethylene glycol, KOtBu. 110° C.;
d) NaH, THF then 5-bromo-2-chloropyrimidine, 70° C.;
e) Pyridine-2-carbonyl azide, CHCl3, 70° C., 2 h then Example 47, 70° C., 16 h.

For further experimental descriptions see [1], [2], [3], [5], [6] and [9].

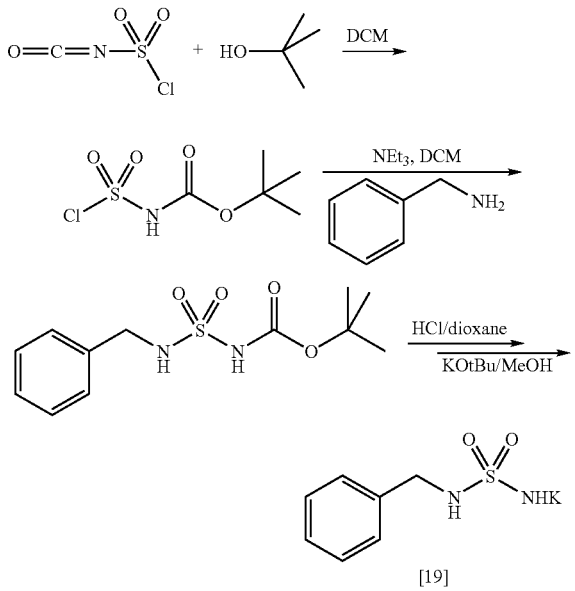
Scheme 3: Preparation of the sulfamide-moieties [10], [11], [12], [13], [14], [15] and [19] and preparation of substituted pyrimidines [16], [17]:

a)



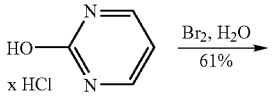
8

b)

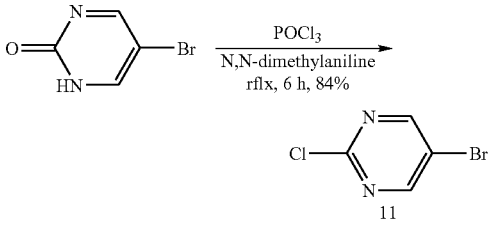


[19]

c)

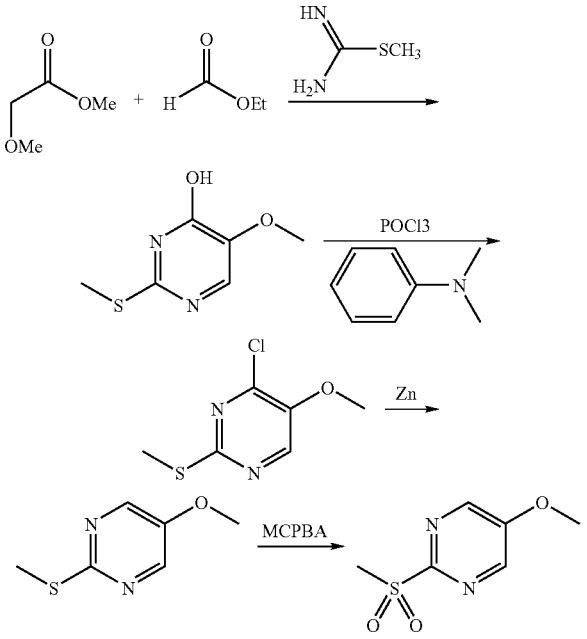


-continued

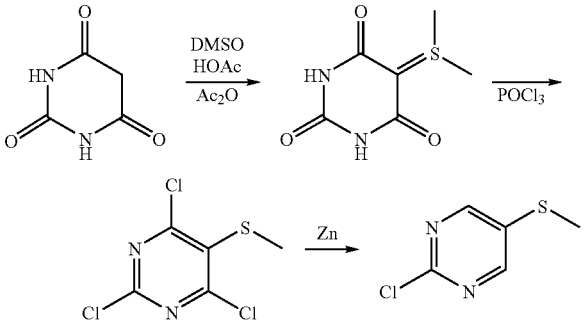


11

d)

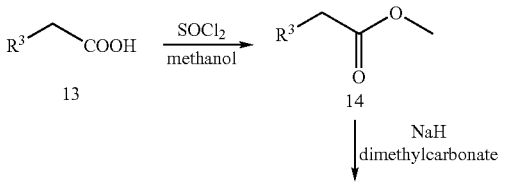


e)

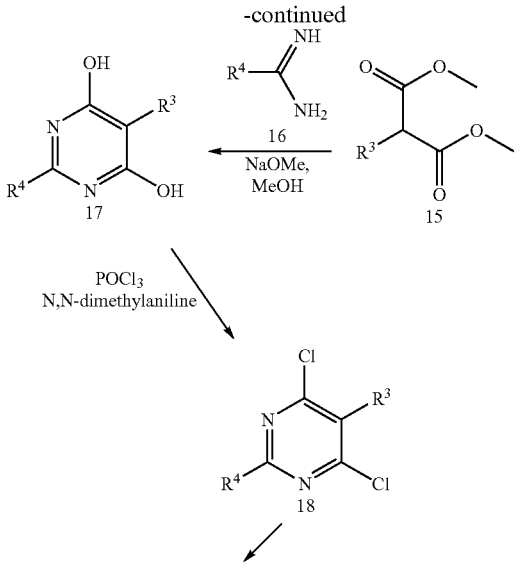


For further experimental descriptions see [1], [2], [3], [5], [6].

Scheme 4: Preparation of the precursors for the synthesis of compounds of general formula I wherein X represents a bond [5], [18]:



13 14



In Scheme 4 the symbols represent the same as defined in general formula I above.

[1] W. Göhring, J. Schildknecht, M. Federspiel; *Chimia*, 1996, 50, 538–543.

[2] W. Neidhart, V. Breu, D. Bur, K. Burri, M. Clozel, G. Hirth, M. Müller, H. P. Wessel, H. Ramuz; *Chimia*, 1996, 50, 519–524 and references cited there.

[3] W. Neidhart, V. Breu, K. Burri, M. Clozel, G. Hirth, U. Klinkhammer, T. Giller, H. Ramuz; *Bioorg. Med. Chem. Lett*., 1997, 7, 2223–2228. R. A. Nugent, S. T. Schlachter, M. J. Murphy, G. J. Cleek, T. J. Poel, D. G. Whishka, D. R. Graber, Y. Yagi, B. J. Keiser, R. A. Olmsted, L. A. Kopta, S. M. Swaney, S. M. Poppe, J. Morris, W. G. Tarpley, R. C. Thomas; *J. Med. Chem*., 1998, 41, 3793–3803.

[4] J. March; *Advanced Organic Chemistry*, 4th Ed., 1994, p. 499 and references cited there.

[5] EP 0 743 307 A1; EP 0 658 548 B1; EP 0 959 072 A1 (Tanabe Seiyaku)

[6] EP 0 633 259 B1; EP 0 526 708 A1; WO 96/19459 (F. Hoffmann-LaRoche)

[7] for the Synthesis of 5-membered heterocycles see: Y. Kohara et al; *J. Med. Chem*., 1996, 39, 5228–5235 and references cited there.

[8] EP 0 882 719 A1 (Yamanouchi Pharmaceutical Co., Ltd)

[9] a) R. Graf; *Chem. Ber*., 1959, 92, 509–513. b) G. Weiss, G. Schulze; *Liebigs Ann. Chem*., 1969, 729, 40–51. c) J. A. Kloek, K. L. Leschinsky, *J. Org. Chem*., 1976, 41, 4028–4029. d) R. P. Dickinson, K. N. Dack, C. J. Long, J. Steele; *J. Med. Chem*., 1997, 40, 3442–3452. e) E. Cohen, B. Klarberg; *J. Am. Chem. Soc*, 1962, 84, 1994–2002.

[10] E. Cohen, B. Klarberg; *J. Am. Chem. Soc*., 1962, 84, 1994.

[11] G. Weiss, G. Schulze, *Liebigs Ann. Chem*., 1969, 729, 40.

[12] R. Graf, *Chem. Ber*., 1959, 92, 509.

[13] J. A. Kloek, K. L. Leschinsky, *J. Org. Chem*., 1976, 41, 4028.

[14] R. E. Olson, T. M. Sielecki, et al; *J. Med. Chem*., 1999; 42, 1178.

[15] R. P. Dickinson, K. N. Dack, et al; *J. Med. Chem*., 1997; 40, 3442.

[16] D. G. Crosby, R. V. Berthold; *J. Org. Chem*., 1960; 25; 1916.

[17] Bayer A G (Maurer, F.; Hammann, I.; Behrenz, W.); U.S. Pat. No. 4,233,294 1980.

[18] E. D. Morgan; *Tetrahedron*, 1967, 23, 1735.

[19] M. J. Tozer, I. M. Buck et al.; *Bioorg. Med. Chem. Lett*., 1999, 9, 3103. G. Dewynter et al.; *Tetrahedron*, 1993, 49, 65.

EXAMPLES

The following examples illustrate the invention. All temperatures are stated in ° C.

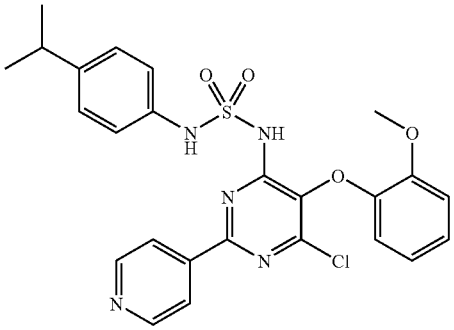
List of Abbreviations:

EtOAc	ethyl acetate
CyHex	cyclohexane
Hex	hexane
DMSO	dimethylsulfoxide
THF	tetrahydrofuran
MCPBA	m-chloroperbenzoic acid
DMF	dimethylformamide
DCM	dichloromethane
HV	high vacuum conditions
rt	room temperature
t_R	retention time
min	minutes
DBU	1,8-diazabicyclo[5.4.0]undec-7-en(1,5-5)
DMAP	4-dimethylaminopyridine
rflx	reflux

The following compounds were prepared according to the procedure described above and shown in Schemes 1 to 4. All compounds were characterized by 1H-NMR (300 MHz) and occasionally by 13C-NMR (75 MHz) (Varian Oxford, 300 MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s=singlet, d=doublet, t=triplet; m=multiplet), by LC-MS (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Column: 2×30 mm, Gromsil ODS4, 3 µm, 120A; Gradient: 0–100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45 ml/min; t_R is given in min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}) and occasionally by melting point.

Referential Examples (Synthesis of the Precursors)

Referential Example 1



a) To a solution of sodium (0.23 g) in methanol (40 ml) was added 4-cyanopyridine (10.62 g) at r.t. Stirring was continued for 6 h followed by the addition of ammonium-chloride (5.9 g) and stirring was continued for another 10 h. Then, diethylether (120 ml) was added and the precipitate was filtered off after 30 min and washed with diethylether (20 ml). The product was dried under high vacuum. 4-Amidino-pyridine hydrochloride (14.95 g) was obtained as a white powder.

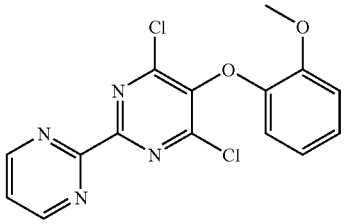
b) 2-Methoxy-phenol (guaiacol) (48 ml) was slowly added to a stirred suspension of potassium carbonate (70.8 g) in acetone (480 ml) followed by heating to 45° C. Then, dimethylchloromalonate (63.2 ml) in acetone (50 ml) was added within 20 min. The reaction mixture was heated to reflux for 16 h. The solvent was evaporated under reduced pressure, the residue taken into water and extracted with DCM. The combined organic layers were dried over sodium sulfate and evaporated. The oily product was crystallized from tert.-butyl-methyl-ether. Dimethyl-(o-methoxyphenoxy)malonate (86 g) was obtained.

c) To a stirred solution of sodium methylate (9.7 g) in methanol (100 ml) a solution of dimethyl-(o-methoxyphenoxy)malonate (21.7 g) in methanol (50 ml) was added within 15 min and stirring was continued for 30 min followed by the addition of 4-amidino-pyridine hydrochlorid (15.0 g) and stirring at r.t. for 20 h. The reaction mixture was concentrated in vacuo. The solid residue was stirred with ether. The obtained powder was filtered off and dissolved in water (300 ml). Acetic acid was added to pH=4. The precipitated product was filtered off, washed with water and dried in vacuo at 50° C. 5-(o-Methoxyphenoxy)-4,6-dihydroxy-2-(4-pyridyl)-pyrimidine (20.1 g) (is possibly also present as the tautomeric 5-(o-methoxyphenoxy)-2-(4-pyridyl)-tetrahydropyrimidine-4,6-dion) was obtained as a white powder.

d) 5-(o-Methoxyphenoxy)-4,6-dihydroxy-2-(4-pyridyl)-pyrimidine (10 g), N-diisopropylethylamine (11.2 g), tetraethylammoniumchloride (11 g) and phosphorus pentachloride (13.8 g) were dissolved in phosphorus oxychloride (25 ml) and heated to reflux for 3 h. The mixture was evaporated in vacuo, toluene was added and the mixture was again evaporated. The residue was taken into DCM and poured onto ice/water. The layers were separated, the organic layer was washed with water, dried over sodium sulfate and evaporated. After recrystallization from acetone, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (6.52 g) was obtained.

e) To a solution of 4-i-propyl-phenyl sulfamic acid amide (642 mg; Referential Example 17) in DMF (9 ml) was added sodium hydride (250 mg). The mixture was warmed to 45° C. for 30 min. Then, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (1.044 g) was added and the reaction mixture was stirred for 60 h at r.t. After acidic work up and chromatography over silicagel with Hex/EtOAc=2/5, 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (0.42 g) can be isolated.

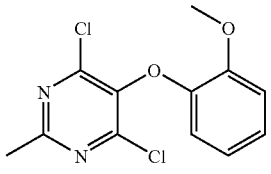
Referential Example 2



a) 4,6-Dihydroxy-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidine [or its tautomer 5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-tetrahydropyrimidine-4,6-dion-] was prepared as disclosed in EP 0 526 708 A1 from 2-amidino-pyrimidine and dimethyl-(o-methoxyphenoxy)malonate.

b) 4,6-Dichloro-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidine was prepared as disclosed in EP 0 526 708 A1 from 4,6-dihydroxy-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidine (which may also be present in the tautomeric form 5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-tetrahydro-pyrimidine-4,6-dione).

Referential Example 3

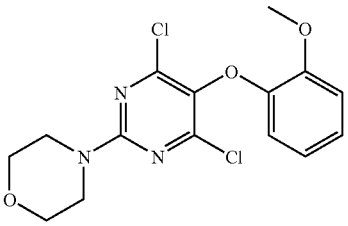


a) A solution of dimethyl-(o-methoxyphenoxy)malonate (10 g) in dry methanol (80 ml) was cooled to 0° C. Sodium methylate (6.71 g) was added portionwise. To the suspension was added of acetamidine hydrochloride (2.84 g) and the mixture was stirred overnight at r.t. The solvent was removed under reduced pressure and the residue was suspended in diethyl ether (100 ml). The solid was filtered off, washed with another portion of diethyl ether (100 ml) and dissolved in water (50 ml). The pH was adjusted to 4 by adding glacial acetic acid (25 ml). The white precipitate that formed was filtered off, washed with water and dried to yield 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-methyl-pyrimidine (5.17 g) (or a tautomer) as a white powder.

b) A solution of 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-methyl-pyrimidine (10.9 g) (or a tautomer) in $POCl_3$ (150

ml) was stirred at 50° C. for 72 h. The excess of $POCl_3$ was evaporated, toluene was added to coevaporate traces of $POCl_3$. Eventually, an ice/water mixture was carefully added to the residue and the pH was adjusted to 8 using 3 N sodium hydroxide solution. The mixture was further diluted with water (300 ml) and extracted with DCM (500 ml). The organic layer was separated, washed with water (300 ml), dried over Na_2SO_4 and evaporated. The residue was dissolved again in DCM and filtered through a pad of silica gel eluting with DCM. The solvent was removed in vacuo. The resulting residue was dried to furnish 4,6-dichloro-5-(o-methoxyphenoxy)-2-methyl-pyrimidine (8.7 g) as a beige powder.

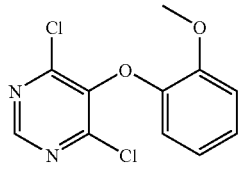
Referential Example 4



a) A solution of dimethyl-(o-methoxyphenoxy)malonate (32.75 g) in methanol (250 ml) was cooled to 0° C. Sodium methylate (20.0 g) was added portionwise and upon completion of the addition the mixture was stirred at r.t. for 6 h. Then morpholinoformamidine hydrobromide (25.0 g) was added and stirring was continued for 72 h. The solvent of the beige suspension was evaporated and the residue was washed twice with diethyl ether (150 ml). The remaining powder was dissolved in water (200 ml). Upon adjusting the pH to 4 with acetic acid (50 ml) a precipitate formed. The precipitate was collected, washed with water and dried under high vacuum to yield 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-(N-morpholino)-pyrimidine (17.01 g) (or a tautomer) as a slightly beige powder.

b) At 0° C. $POCl_3$ (50 ml) was carefully added to Hünig's base (27.5 ml). To this mixture 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-(N-morpholino)-pyrimidine (17 g) was added portionwise. The resulting mixture was stirred over night at 130° C. The excess of reagents was evaporated and traces of $POCl_3$ were removed by coevaporation with toluene. The black residue was treated with DCM (50 ml) and a water/ice mixture (50 ml). After stirring for 15 min, the mixture was diluted with water (400 ml) and DCM (400 ml). The organic layer was separated and washed with water (300 ml). The aqueous layer was extracted with DCM (400 ml). The combined DCM layers were dried over Na_2SO_4 and the solvent was removed to a volume of about 100 ml. The remaining solution was filtered over silica gel (50 g) eluting with DCM. The filtrate was evaporated. The resulting residue was suspended in diethyl ether (50 ml). The solid was filtered off and dried to give 4,6-dichloro-5-(o-methoxyphenoxy)-2-(N-morpholino)-pyrimidine (13.85 g) as a white crystalline powder.

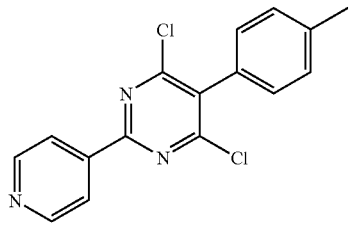
Referential Example 5



a) At 5° C. sodium methylate (12.7 g) was added portionwise to a solution of dimethyl-(o-methoxyphenoxy)malonate (18.9 g) in methanol (450 ml). Upon completion of the addition stirring was continued at r.t. for 30 min followed by the addition of formamidine hydrochloride (6 g). The mixture was stirred at r.t. for 72 h. Eventually, the solvent was removed under reduced pressure and the remaining residue was suspended in diethyl ether. The solid material was filtered off and dissolved in water (100 ml). The solution was acidified with conc. hydrochloric acid. A white precipitate formed. The precipitate was collected, washed with water and dried to give 5-(o-methoxyphenoxy)-4,6-dihydroxy-pyrimidine (15.1 g) (or a tautomer) as a white powder.

b) To a solution of 5-(o-methoxyphenoxy)-4,6-dihydroxy-pyrimidine (7.5 g) in $POCl_3$ (90 ml) N,N-dimethylaniline (24 ml) was added. The mixture was heated to 160° C. and stirred for 2.5 h. Excess of $POCl_3$ was distilled off under reduced pressure. Traces of $POCl_3$ were coevaporated with toluene. The remaining oil was treated with a water:ice mixture. The mixture was acidified with 1 N hydrochloric acid and extracted twice with diethyl ether. The combinded organic layers were washed twice with dilute aqueous hydrochloric acid, dried over $MgSO_4$ and evaporated. The remaining solid was washed with methanol and dried. This gave 4,6-dichloro-5-(o-methoxyphenoxy)-pyrimidine (4.75 g) as a pale yellow powder.

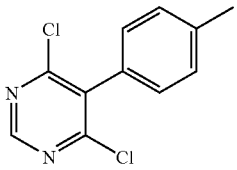
Referential Example 6



a) A solution of sodium methylate (6.8 g) in methanol (200 ml) was cooled to 0° C. A solution of diethyl 2-(p-tolyl)-malonate (10.3 g) in methanol (50 ml) was slowly added. Upon completion of the addition the solution was allowed to warm to r.t. and 4-amidino-pyridine hydrochloride (7.57 g) was added. The mixture was stirred at r.t. for 16 h. Eventually, the solvent was removed under reduced pressure and the remaining residue was dissolved in 2 M hydrochloric acid. The solution was extracted with diethyl ether, then adjusted to pH 5 with 10 M sodium hydroxide solution. A precipitate formed. The precipitate was collected, washed with cold water and dried at 60° C. under high vacuum. This gave 4,6-dihydroxy-2-(4-pyridyl)-5-(p-tolyl)-pyrimidine (8.77 g) (or a tautomer) as orange crystals.

b) To a mixture of 4,6-dihydroxy-2-(4-pyridyl)-5-(p-tolyl)-pyrimidine (8.0 g) and $POCl_3$ (100 ml) diethylamine (25 ml) was added at r.t. The mixture was stirred for 16 h at 60° C. The excess of $POCl_3$ was distilled off under reduced pressure. The remaining oil was dissolved in DCM (300 ml) and treated with water (300 ml). The aqueous layer was separated and extracted three times with DCM. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated. The resulting residue was suspended in isopropanol. The solid material was collected, washed with isopropanol and diethyl ether and dried to give 4,6-dichloro-2-(4-pyridyl)-5-(p-tolyl)-pyrimidine (7.2 g) as a white crystalline powder.

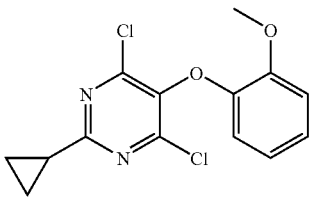
Referential Example 7



a) At 0° C. a solution of diethyl 2-(p-tolyl)-malonate (14.2 g) in methanol (50 ml) was slowly added to a solution of sodium methylate (9.4 g) in methanol (300 ml). Upon completion of the addition the reaction mixture was allowed to warm up and formamidine hydrochloride (5.4 g) was added. The mixture was stirred at r.t. for 16 h. The solvent was removed under reduced pressure and the remaining residue was treated with 2 N hydrochloric acid (150 ml). The suspension was stirred for 0.5 h. At 0–5° C., the pH was carefully adjusted to 4 using 10 N sodium hydroxide solution. The precipitate was collected, washed with cold water, isopropanol, and diethyl ether and dried under high vacuum at 65° C. to give 4,6-dihydroxy-5-(p-tolyl)-pyrimidine (11.2 g) (or a tautomer) as a white powder.

b) At r.t. N,N-dimethylaniline (10 ml) was added to a mixture of 4,6-dihydroxy-5-(p-tolyl)-pyrimidine (5.1 g) and $POCl_3$ (75 ml). The reaction mixture was stirred at 70° C. for 16 h. The excess of $POCl_3$ was distilled off and the remaining oil was treated with an ice:water mixture and extracted three times with diethyl ether. The combined organic layers were washed with 1N aqueous hydrochloric acid followed by brine, dried over $MgSO_4$ and evaporated. The remaining brown oil was crystallised from isopropanol. The pale yellow crystals were collected, washed with cold isopropanol and dried under high vacuum to furnish 4,6-dichloro-5-(p-tolyl)-pyrimidine (4.1 g).

Referential Example 8



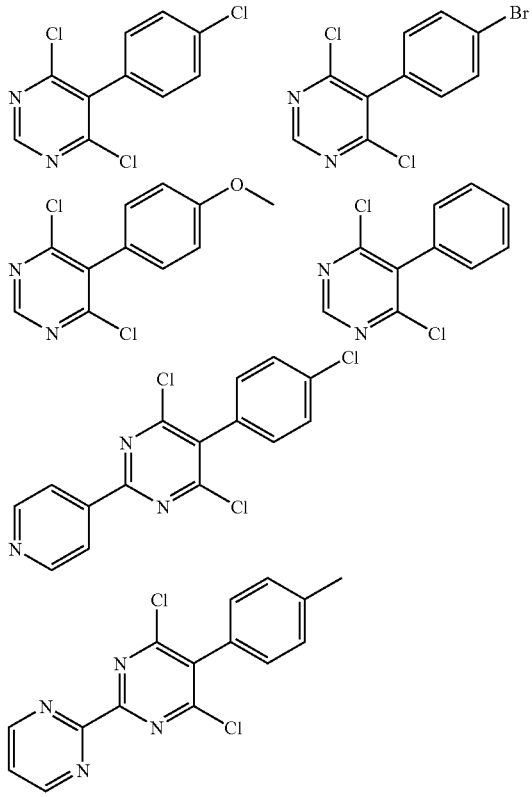
a) To a solution of sodium (5.17 g) in methanol (200 ml) dimethyl-(2-methoxyphenoxy)malonate (21.1 g) was added and the mixture was stirred at r.t. for 30 min. To the slurry, cyclopropylamidine hydrochloride (12.0 g) was added.

The mixture was stirred at r.t. for 22 h. Eventually, the solvent was removed in vacuo. The remaining residue was suspended in diethyl ether (250 ml). The diethyl ether was decanted and the remaining solid was dissolved in water (250 ml). The solution was acidified with 25% aqueous hydrochloric acid. The precipitate that formed was collected, washed with water and dried at 60° C. under high vacuum to give 5-(2-methoxyphenoxy)-4,6-dihydroxy-2-cyclopropyl-pyrimidine (19.26 g) as a colourless powder. LC-MS: t_R=2.74 min, $[M+1]^+$=275.24, $[M-1]^-$=273.29.

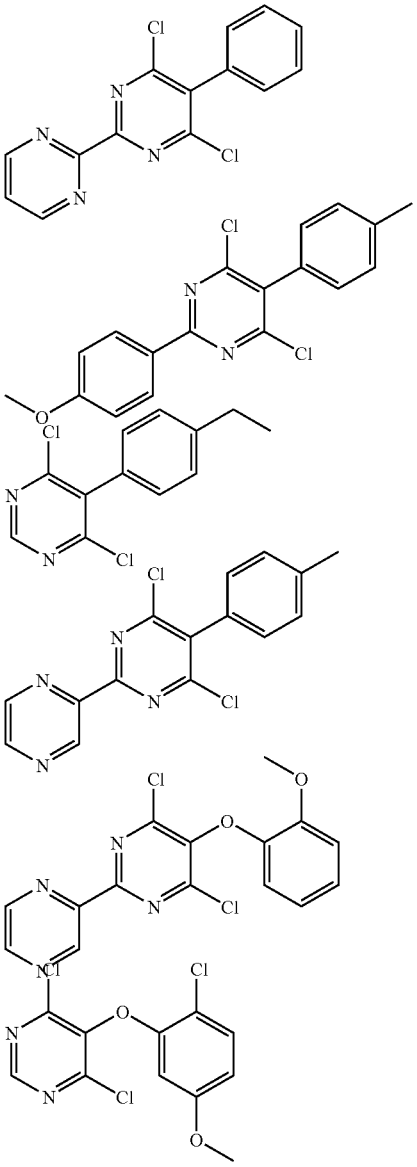
b) To a suspension of 5-(2-methoxyphenoxy)-4,6-dihydroxy-2-cyclopropyl-pyrimidine (8.22 g) in $POCl_3$ (87 ml), N,N-dimethylaniline (12 ml) was added. The mixture became clear and was stirred at 130° C. for 3.5 h. Excess $POCl_3$ was removed in vacuo, remaining traces of $POCl_3$ were coevaporated with toluene. The remaining sirup was poured on an ice-water mixture and the resulting solution was extracted three times with diethyl ether. The organic layers were combined, washed once with 1 N aqueous hydrochloric acid and twice with water, treated with activated charcoal, dried over $MgSO_4$ and evaporated. The residue was crystallised from a diethyl ether/hexane to give 4,6-dichloro-2-cyclopropyl-5-(2-methoxyphenoxy)-pyrimidine (6.64 g) as a beige powder. LC-MS: t_R=5.36 min, $[M+1]^+$=311.19.

Referential Example 9

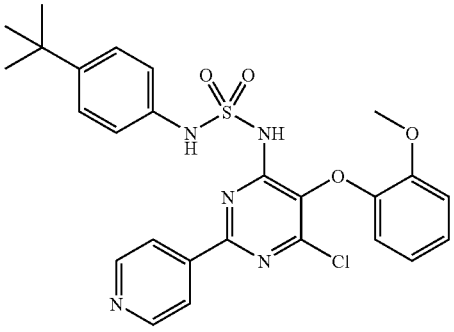
According to procedures described in Referential Examples 1 to 8 and in the literature [2], [3], [5], [6] and [8], the following 4,6-dichloropyrimidine precursors were prepared.



-continued

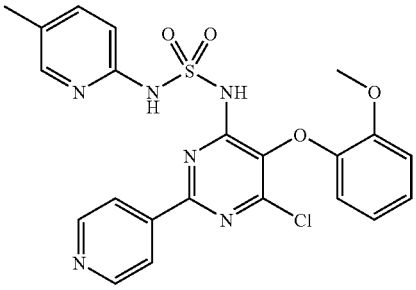


Referential Example 10



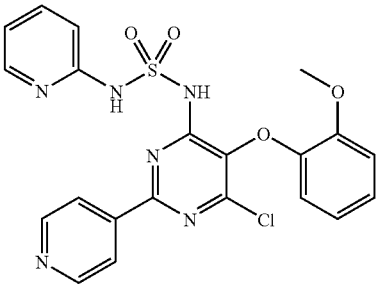
To a solution of 4-t-butyl-phenyl sulfamic acid amide (228 mg, Referential Example 18) in DMF (3 ml) was added sodium hydride (42 mg). Then, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (305 mg) and Hünig base (0.17 ml) was added and the reaction mixture was stirred for 5 h at 60° C. After acidic work up and crystallization, 4-t-butyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (0.15 g) could be isolated. t_R=5.54 min (LC); $[M+H]^+$=540.44 (ES+);

Referential Example 11



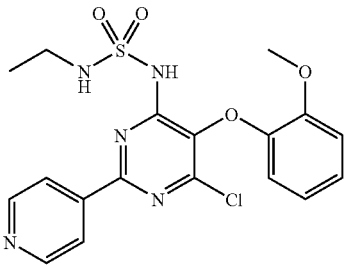
According to the procedure described in referential Example 1e), 5-methyl-pyridine-2-sulfamic acid amide (252 mg, Referential Example 20) was reacted with 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (410 mg, Referential Example 1d)) to give 5-methyl-pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (100 mg). t_R=4.02 min (LC); $[M+H]^+$=499.33 (ES+);

Referential Example 12



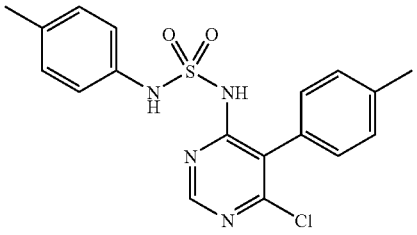
According to the procedure described in referential Example 1e), pyridine-2-sulfamic acid amide (60 mg, Referential Example 21) was reacted with 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (100 mg, Referential Example 1d)) to give pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (100 mg). t_R=3.83 min (LC); $[M-H]^+$=483.33 (ES−);

Referential Example 13



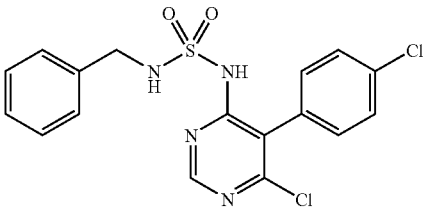
According to the procedure described in referential Example 1e), ethyl-sulfamic acid amide (40 mg, Referential Example 22) was reacted with 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (100 mg, Referential Example 1d)) to give pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (70 mg). t_R=4.40 min (LC); $[M-H]^+$=434.28 (ES−);

Referential Example 14



To 4,6-dichloro-5-p-tolyl-pyrimidine (Referential Example 7) (2.0 g) dissolved in DMSO (35 ml) was added di-isopropyl-ethyl-amine (1.46 ml) followed by addition of 4-methyl-phenyl sulfamic acid amide potassium salt (2.78 g) [prepared from the product described in Referential Example 19 and potassium tert.-butylate in methanol followed by evaporation of the solvent]. The mixture was stirred for 48 h at rt then poured onto water (500 ml) and diethylether (250 ml) was added and the solution was stirred for 30 min. The layers were separated and the water layer was acidified with acetic acid (2.0 ml) and cooled to 0° C. for 1 h. The precipitated product was filtered off and washed with water and diethylether and dried to give 4-methyl-phenyl sulfamic acid-[6-chloro-5-(p-tolyl)-4-pyrimidinyl]-amide (2.02 g). t_R=5.00 min (LC); $[M+H]^+$=389.11 (ES+);

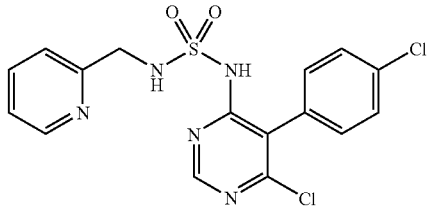
Referential Example 15



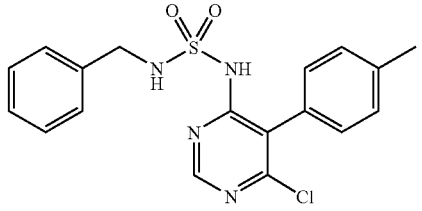
To 4,6-dichloro-5-(4-chloro-phenyl)-pyrimidine (Referential Example 9) (2.59 g) dissolved in DMSO (14 ml) was added di-isopropyl-ethyl-amine (1.8 ml) followed by the addition of benzyl sulfamic acid amide potassium salt (2.25 g) [prepared from the product described in Referential Example 22 and potassium tert.-butylate in methanol followed by the evaporation of the solvent]. The mixture was stirred for 24 h at rt then poured onto water (300 ml) and diethylether (120 ml) was added and the solution was stirred for 30 min. The layers were separated and the water layer was acidified with solid citric acid (pH=3) and cooled to 0° C. for 1 h. The precipitated product was filtered off, washed with water and recrystallized from methanol to give benzyl sulfamic acid-[6-chloro-5-(p-chloro-phenyl)-4-pyrimidinyl]-amide (1.8 g). t_R=4.94 min (LC); $[M+H]^+$410.90 (ES+);

Referential Example 16

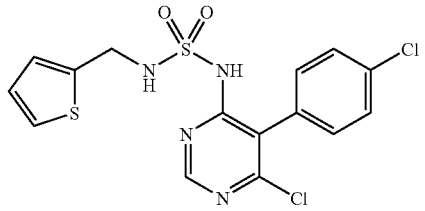
According to the procedure described for the synthesis of Referential Example 15, the following compounds could be prepared:



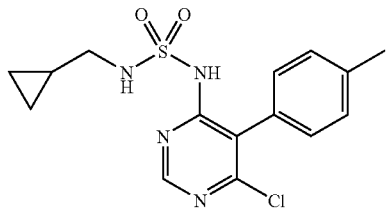
LC-MS: t_R: 4.00; $[M+H]^+$: 411.96



LC-MS: t_R: 4.98; $[M+H]^+$: 389.91

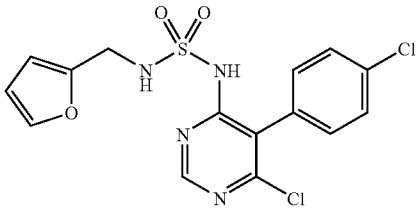


LC-MS: t_R: 4.84; $[M+H]^+$: 414.77

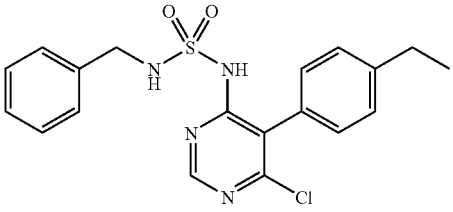


LC-MS: t_R: 4.76; $[M-H]^+$: 351.03

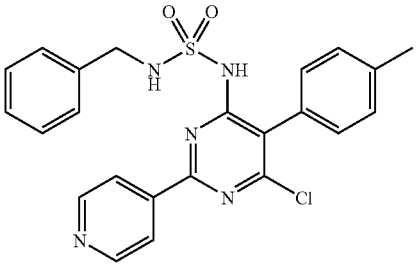
-continued



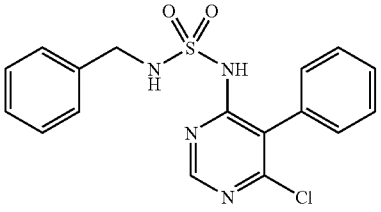
LC-MS: t_R: 4.66; $[M + H]^+$: 400.88



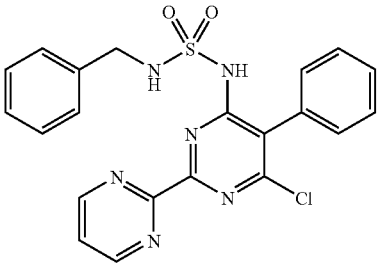
LC-MS: t_R: 5.10; $[M + H]^+$: 403.05



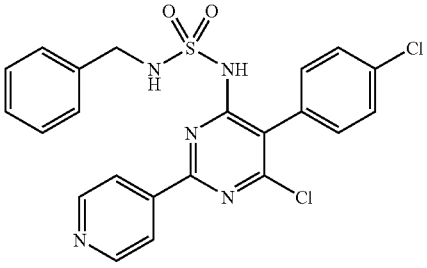
LC-MS: t_R: 4.84; $[M + H]^+$: 466.11



LC-MS: t_R: 4.65; $[M + H]^+$: 375.05

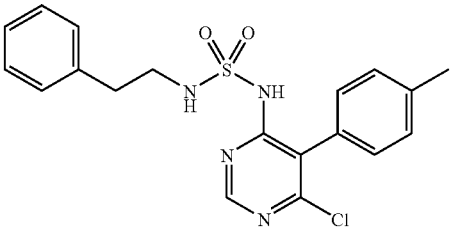


LC-MS: t_R: 4.45; $[M + H]^+$: 453.03

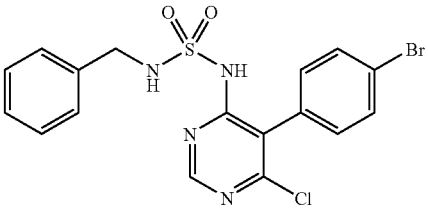


LC-MS: t_R: 5.06; $[M + H]^+$: 486.01

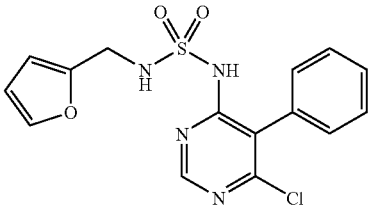
-continued



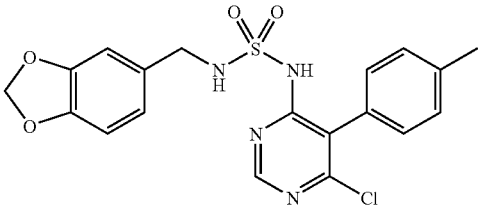
LC-MS: t_R: 5.08; $[M + H]^+$: 403.03



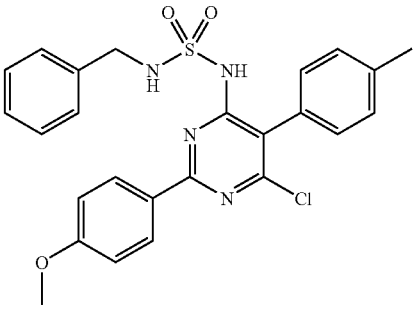
LC-MS: t_R: 5.05; $[M + H]^+$: 454.99



LC-MS: t_R: 4.31; $[M + H]^+$: 365.36

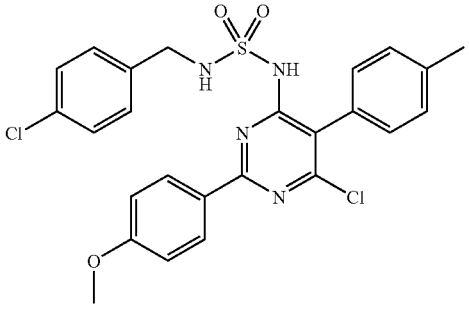


LC-MS: t_R: 4.84; $[M - H]^+$: 433.05

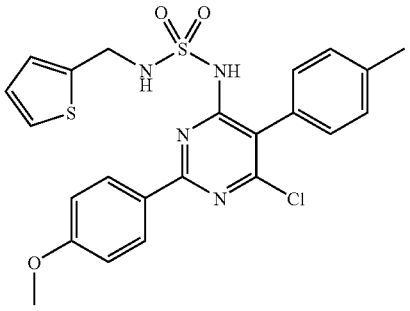


LC-MS: t_R: 6.02; $[M + H]^+$: 495.30

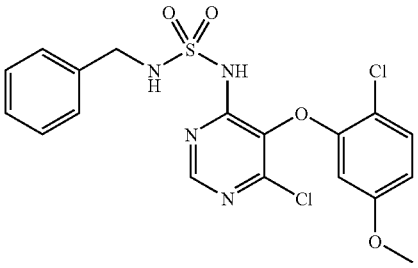
-continued



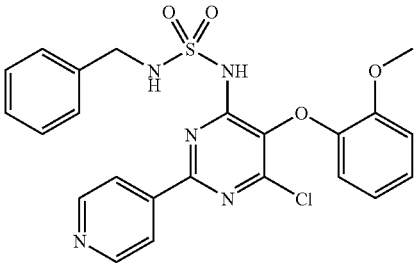
LC-MS: t_R: 6.11; $[M + H]^+$: 529.28



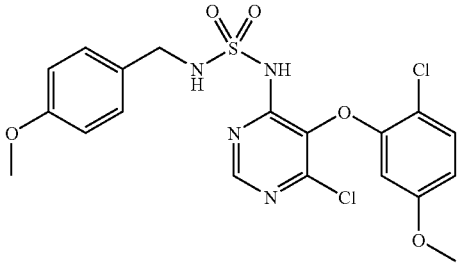
LC-MS: t_R: 5.86; $[M + H]^+$: 501.08



LC-MS: t_R: 5.13; $[M + H]^+$: 456.91

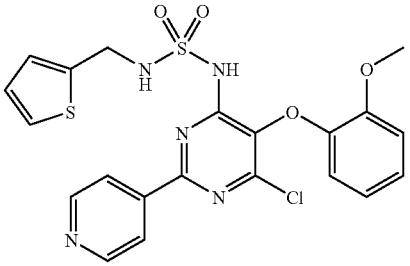


LC-MS: t_R: 4.68; $[M + H]^+$: 498.14

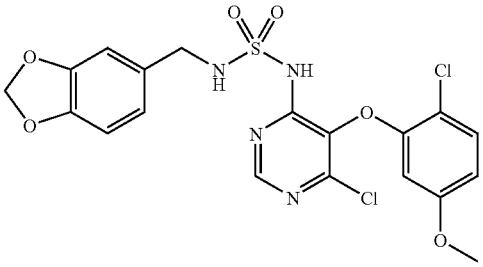


LC-MS: t_R: 4.93; $[M + H]^+$: 484.95

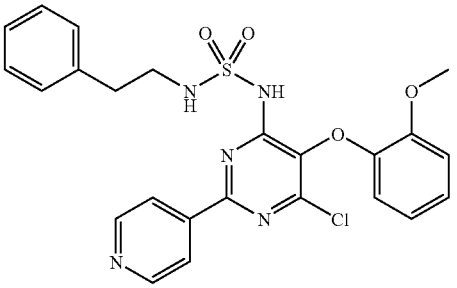
-continued



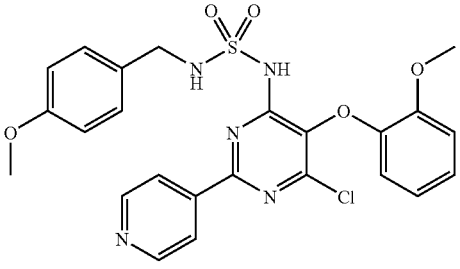
LC-MS: t_R: 4.57; $[M + H]^+$: 504.06



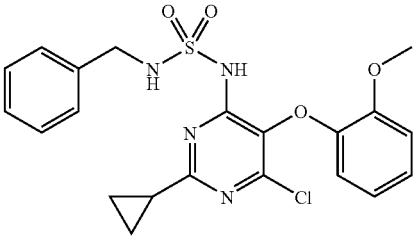
LC-MS: t_R: 4.89; $[M + H]^+$: 499.17



LC-MS: t_R: 4.90; $[M + H]^+$: 512.18

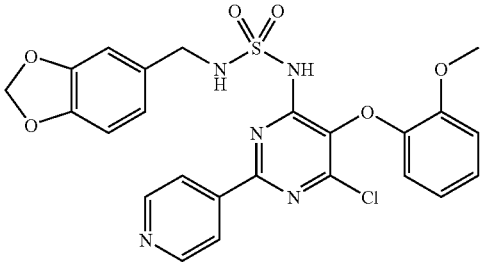


LC-MS: t_R: 4.72; $[M + H]^+$: 527.94

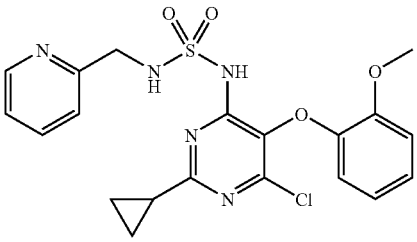


LC-MS: t_R: 5.28; $[M + H]^+$: 461.16

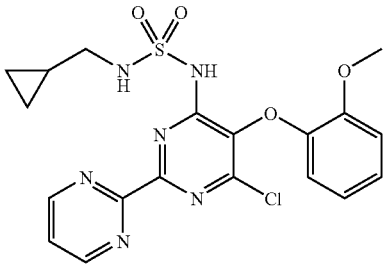
-continued



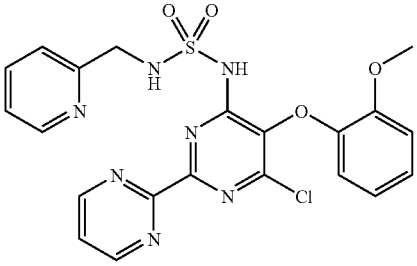
LC-MS: t_R: 4.63; $[M + H]^+$: 542.08



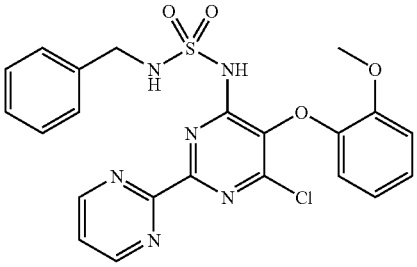
LC-MS: t_R: 3.91; $[M + H]^+$: 462.17



LC-MS: t_R: 4.43; $[M + H]^+$: 463.09

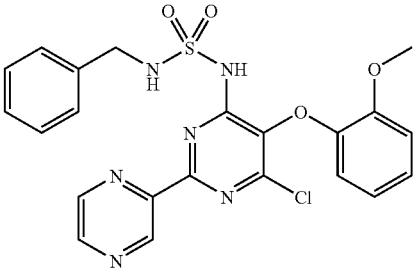


LC-MS: t_R: 3.20; $[M - H]^+$: 497.93

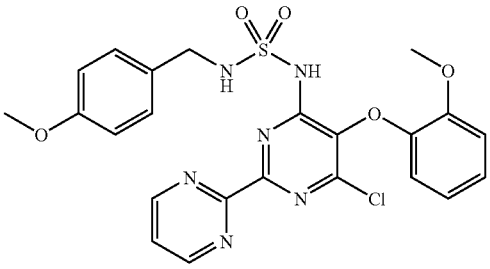


LC-MS: t_R: 4.47; $[M + H]^+$: 499.11

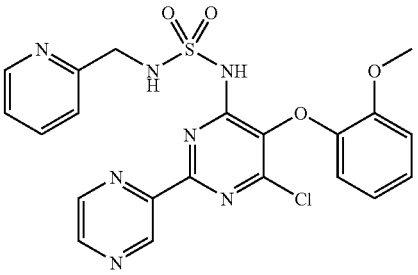
-continued



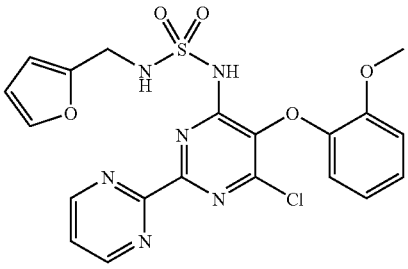
LC-MS: t_R: 4.90; $[M + H]^+$: 499.06



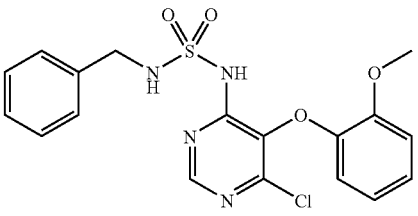
LC-MS: t_R: 4.44; $[M + H]^+$: 529.22



LC-MS: t_R: 3.94; $[M + H]^+$: 500.06

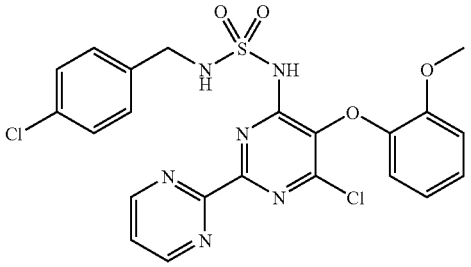


LC-MS: t_R: 4.33; $[M + H]^+$: 489.51

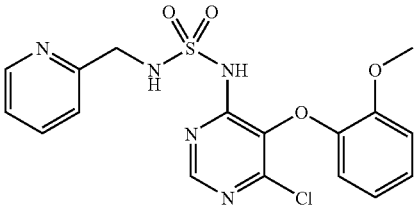


LC-MS: t_R: 4.68; $[M + H]^+$: 421.09

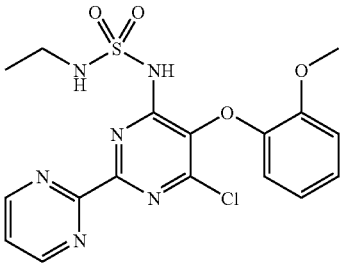
-continued



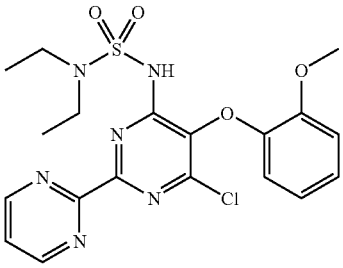
LC-MS: t_R: 4.74; $[M + H]^+$: 535.06



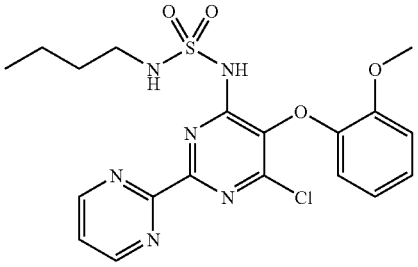
LC-MS: t_R: 3.70; $[M + H]^+$: 423.05



LC-MS: t_R: 3.98; $[M + H]^+$: 437.07

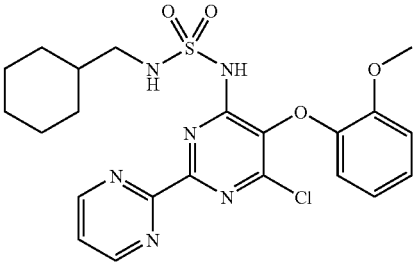


LC-MS: t_R: 4.53; $[M + H]^+$: 465.22

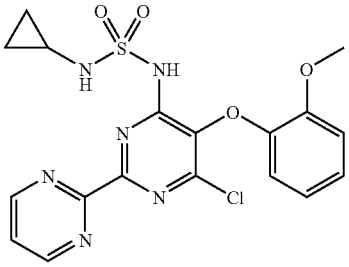


LC-MS: t_R: 5.51; $[M + H]^+$: 465.15

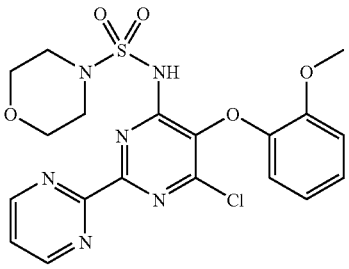
-continued



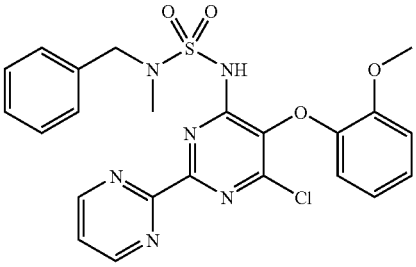
LC-MS: t_R: 5.14; $[M + H]^+$: 505.20



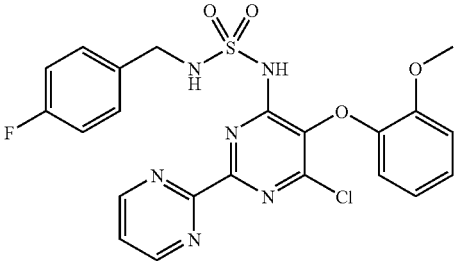
LC-MS: t_R: 4.23; $[M + H]^+$: 449.17



LC-MS: t_R: 4.08; $[M + H]^+$: 479.22

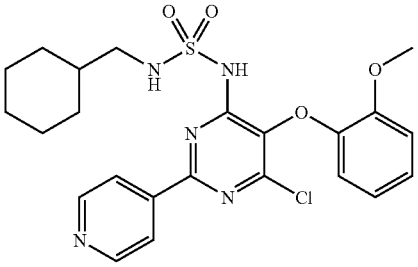


LC-MS: t_R: 5.07; $[M + H]^+$: 513.19

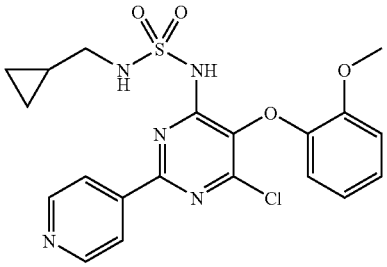


LC-MS: t_R: 4.67; $[M + H]^+$: 517.26

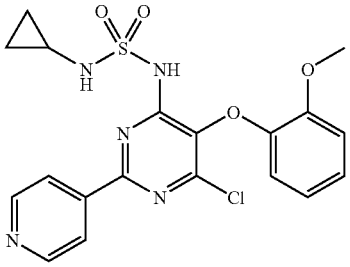
-continued



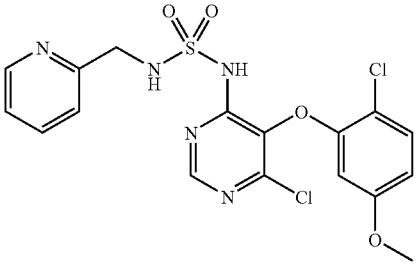
LC-MS: t_R: 5.36; $[M + H]^+$: 505.63



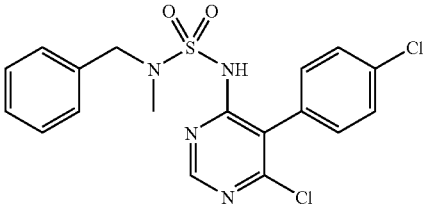
LC-MS: t_R: 4.69; $[M + H]^+$: 462.23



LC-MS: t_R: 4.38; $[M + H]^+$: 448.27

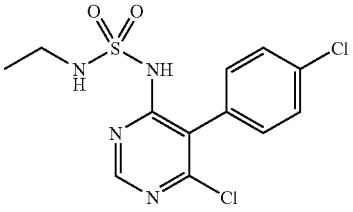


LC-MS: t_R: 4.09; $[M + H]^+$: 456.21

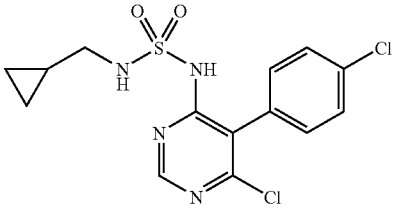


LC-MS: t_R: 5.48; $[M + H]^+$: 424.80

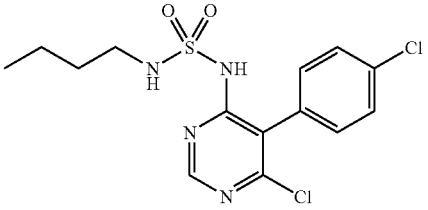
-continued



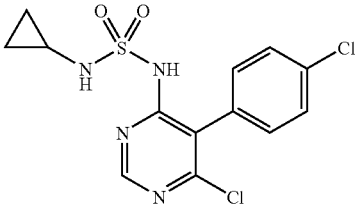
LC-MS: t_R: 4.42; $[M + H]^+$: 347.03



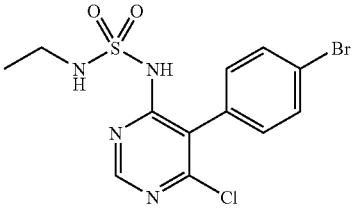
LC-MS: t_R: 4.85; $[M + H]^+$: 375.03



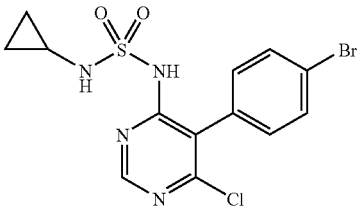
LC-MS: t_R: 4.94; $[M + H]^+$: 376.65



LC-MS: t_R: 4.61; $[M + H]^+$: 360.99



LC-MS: t_R: 4.41; $[M + H]^+$: 392.95

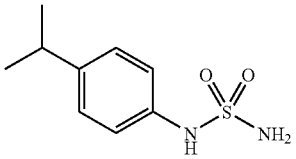


LC-MS: t_R: 4.94; $[M + H]^+$: 404.97

Synthesis of the Sulfamic Acid Amides:

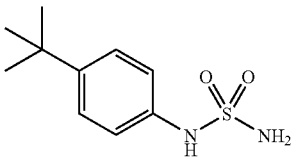
Sulfamoylchloride (NH_2—SO_2—Cl) was prepared according to the procedure given in the literature [11] and [12].

Referential Example 17



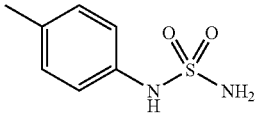
To a solution of sulfamoylchloride in benzene (0.09 mol in 70 ml) was added 4-i-propyl aniline (25.6 ml) via addition funnel at 0° C. The suspension was diluted with benzene (80 ml) and stirred for 20 min. $NaOH_{aq}$ (36 ml; 5 N) was added and the suspension was thoroughly shaken. EtOAc (500 ml) was added and under ice cooling conc. hydrochloric acid was added until pH=6. The water was separated and the EtOAc was evaporated. The brown residue was shaken twice with hexane followed by the addition of a sodium hydroxide solution (5 N). The mixture was extracted three times with diethylether. The water layer was cooled to 0° C. and the pH adjusted to 2 by the addition of conc. hydrochloric acid. The product precipitated and was filtered off and washed with cold water. After high vacuum drying 4-isopropyl-phenyl-sulfamic acid amide was obtained (3.47 g).

Referential Example 18



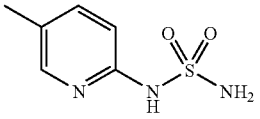
According to the procedure described in Referential Example 17, 4-tert.-butylphenyl-sulfamic acid amide was prepared.

Referential Example 19



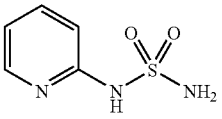
According to the procedure described in Referential Example 17, 4-methyl-phenyl-sulfamic acid amide was prepared.

Referential Example 20



To a solution of 2-amino-5-methyl-pyridine (3.24 g) in THF (30 ml) was added sodium hydride (1.2 g; 60% disperison in mineral oil). The mixture was warmed to 45° C. for 30 min. After cooling to 10° C. a solution of sulfamoylchloride in diethylether (0.0445 mol in 62.5 ml) was added within 30 min followed by stirring for 30 min at r.t. and evaporation of the solvent. To the residue was added a sodium hydroxide solution (5 N, 15 ml). The mixture was extracted several times with toluene. The water layer was cooled to 0° C. and the pH was adjusted to 7 by the addition of conc. hydrochloric acid. The product crystallized and was filtered off to give 5-methyl-pyridine-2-sufamic acid amide (1.1 g).

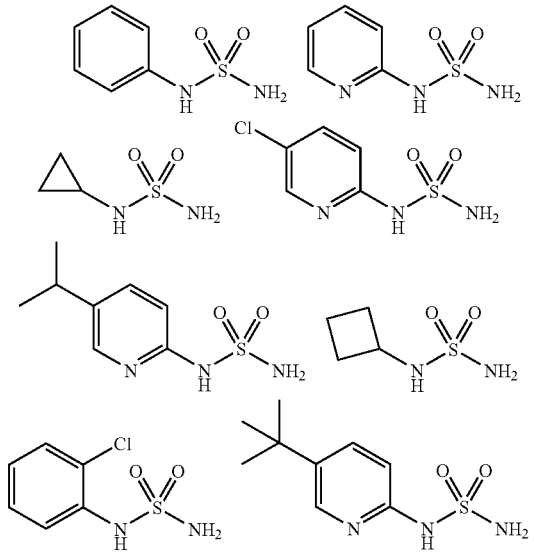
Referential Example 21



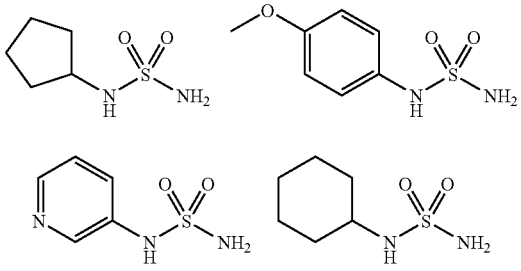
According to the procedure described in Referential Example 20, pyridine-2-sulfamic acid amide was prepared.

Further cycloalkyl-, aryl- or heteroaryl-sulfamic acid amides (as given by the formulae in FIG. 1) can be prepared according to the procedure described in Referential Example 17 (for cycloalkyl and aryl derivatives) or according to the procedure described in Referential Example 21 (for heteroaryl derivatives) or according to the procedure described in Referential Example 22 (for cycloalkyl derivatives).

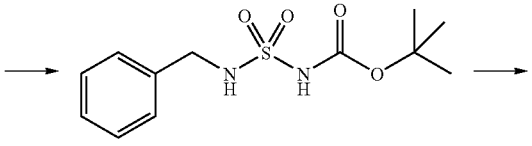
Figure 1:



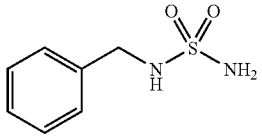
-continued



Referential Example 22: [19]



ZP1



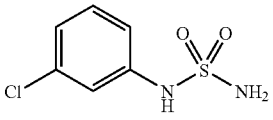
Benzylsulfamide

a) Chlorosulfonylisocyanate (14.14 g) was dissolved in DCM (50 ml) and cooled to 0° C. A solution of tert.-butanol (9.6 ml) in DCM (50 ml) was added within 30 minutes. Stirring was continued for additional 30 minutes at rt.

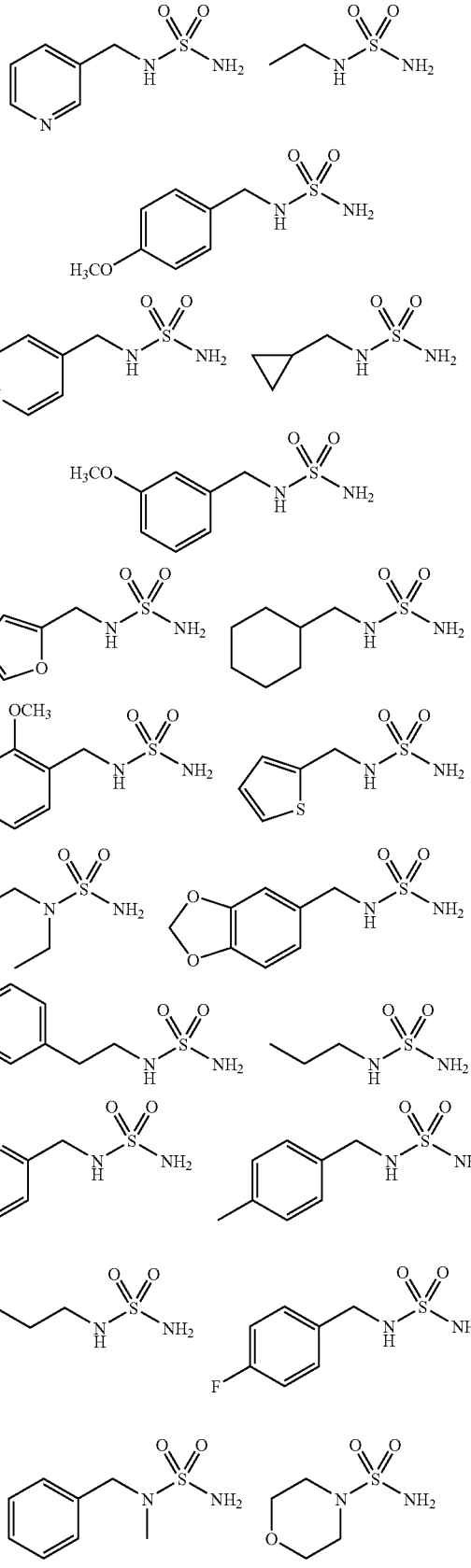
b) The solution prepared as described under a) was then added at 0° C. within 1 h to a solution of benzylamine (10.7 g) and triethylamine (15.32 ml) in DCM (200 ml). Stirring was continued for 10 h at rt; The mixture was concentrated in vacuo, taken into EtOAc (500 ml) and washed with water (2 times 40 ml) and brine (30 ml), dried with magnesium sulfate and again concentrated in vacuo. The crude material was crystallized from EtOAc and dried at HV to give ZP1 (13.68 g). ZP1 was dissolved in dioxane (20 ml) and 120 ml 4 M HCl in dioxane was added within 1 h at rt. Stirring was continued for 8 h followed by complete evaporation of the solvents and drying at HV to give benzylsulfamide (9.47 g).

Further —HN—CH_2-aryl/—HN—CH_2-heteroaryl/—HN—CH_2-alkyl/—HN—CH_2-cycloalkyl/—HN—CH_2-heterocyclyl and other sulfamic acid amides (as given by the formulae in FIG. 2) can be prepared according to the procedure described in Referential Example 22.

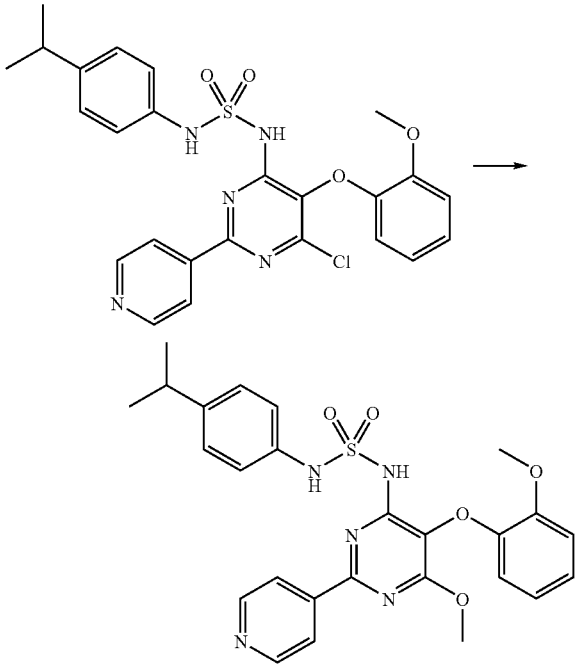
Figure 2:



-continued

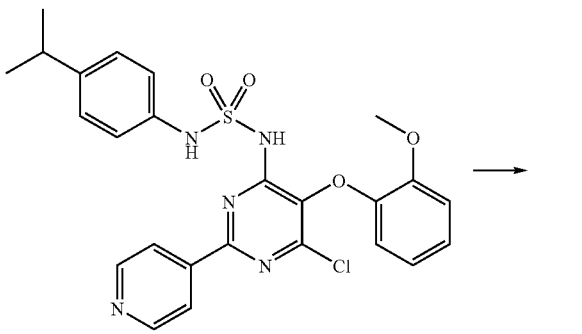


Example 1

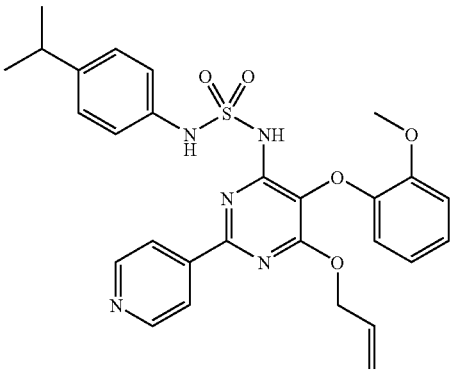


To a mixture of methanol (1 ml) and THF (2 ml) was added sodium hydride (100 mg, 60% dispersion in mineral oil) followed by the addition of 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (100 mg, Referential Example 1e)). DMF (0.5 ml) was added and the reaction mixture was heated to 80° C. for 20 h. The solvents were evaporated, water (14 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water to give 4-i-propyl-phenyl sulfamic acid-[6-methoxy-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (100 mg). t_R=5.08 min, (LC); $[M+H]^+$=522.45 (ES+).

Example 2

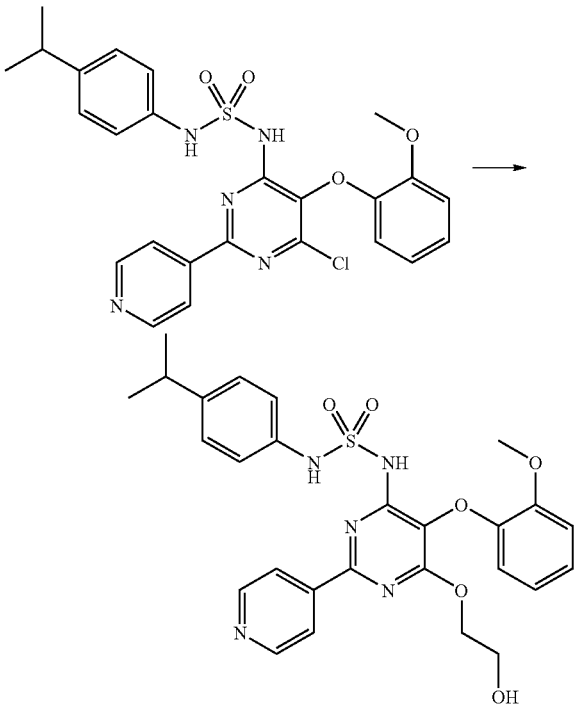


-continued



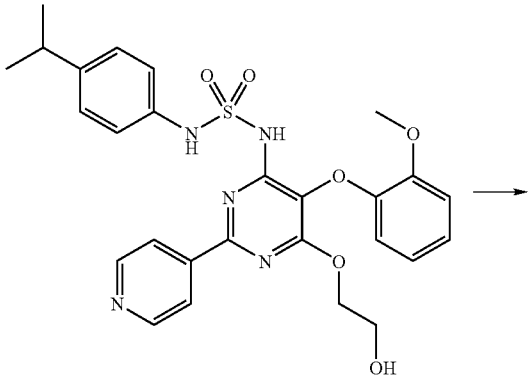
To a mixture of allyl alcohol (1 ml) and THF (2 ml) was added sodium hydride (100 mg, 60% dispersion in mineral oil) followed by the addition of 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (100 mg, Referential Example 1e)). DMF (0.5 ml) was added and the reaction mixture was heated to 80° C. for 20 h. The solvents were evaporated, water (14 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water and purified by chromatography through silicagel with EtOAc/Hex=3:2 to give 4-i-propyl-phenyl sulfamic acid-[6-allyloxy-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (10 mg). t_R=5.36 min, (LC); $[M+H]^+$=548.46 (ES+).

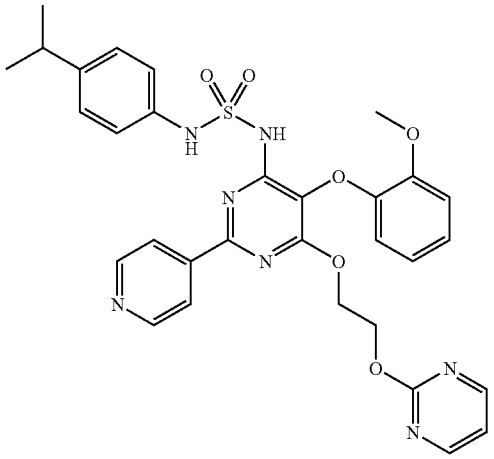
Example 3



Sodium hydride (17 mg, 60% dispersion in mineral oil) was added to ethylene glycol (1.2 ml) followed by addition of dimethoxyethane (0.5 ml). Stirring was continued for 30 min, then 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (45 mg, Referential Example 1e)) was added and the reaction mixture was heated to 80° C. for 48 h. The solvents were evaporated, water (10 ml) and a 10% solution of citric acid was added until the pH was 3 followed by extraction with EtOAc. The organic layers were dried over sodium sulfate and the solvent was evaporated. The crude product was purified by chromatography through silicagel with EtOAc to give 4-i-propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (38 mg). t_R=4.56 min, (LC); $[M+H]^+$=552.36 (ES+).

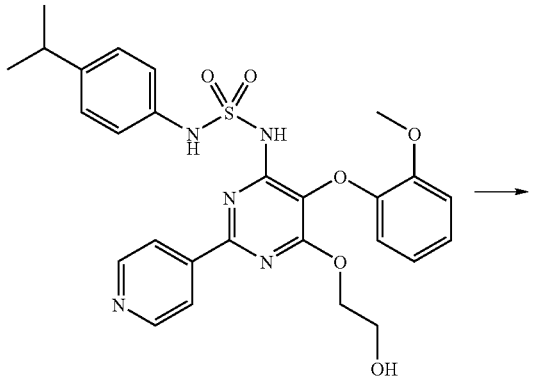
Example 4

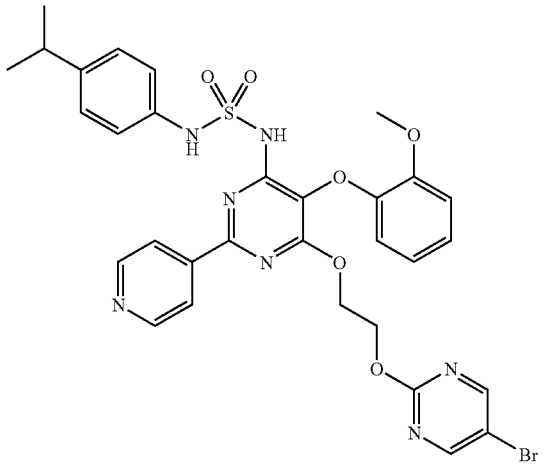




4-i-Propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (60 mg, Example 3) was dissolved in THF (8 ml) and sodium hydride (14 mg, 60% dispersion in mineral oil) was added and stirring continued for 10 min. 2-Chloro-pyrimidine (22 mg) was added and the mixture was heated to 60° C. for 90 min. DMF (0.5 ml) was added and the solution was stirred at r.t. for 48 h. The solvents were evaporated, water (12 ml) and a 10/solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water and purified by recrystallization from diethyl ether to give 4-i-propyl-phenyl sulfamic acid-[6-[2-(pyrimidin-2-yloxy)-ethoxy]-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (50 mg). t_R=4.80 min, (LC); $[M+H]^+$=630.91 (ES+).

Example 5

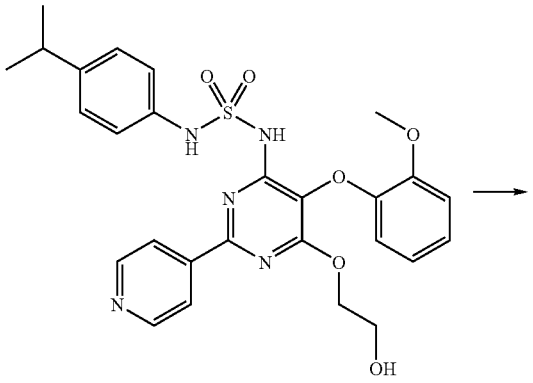




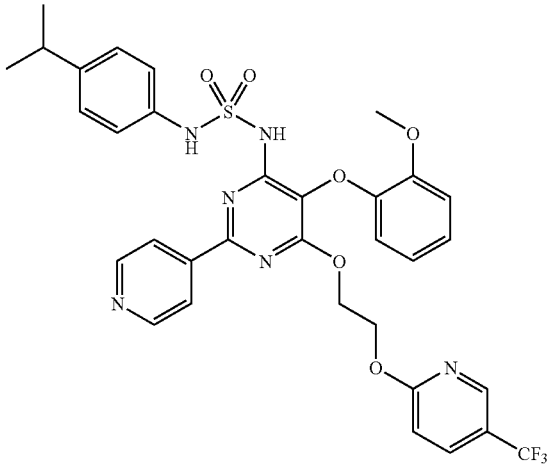
4-i-Propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (60 mg, Example 3) was dissoved in THF (8 ml). Sodium hydride (14 mg, 60% dispersion in mineral oil) was

added and stirring continued for 10 min. 5-Bromo-2-chloro-pyrimidine (37 mg) was added and the mixture was heated to 60° C. for 120 min. DMF (0.5 ml) was added and the solution was stirred at r.t. for 48 h. The solvents were evaporated, water (12 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water and purified by chromatography through silica gel with EtOAc/Hex=1:1 to give 4-i-propyl-phenyl sulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (55.4 mg). t_R=5.30 min, (LC); $[M+H]^+$=710.35 (ES+).

Example 6

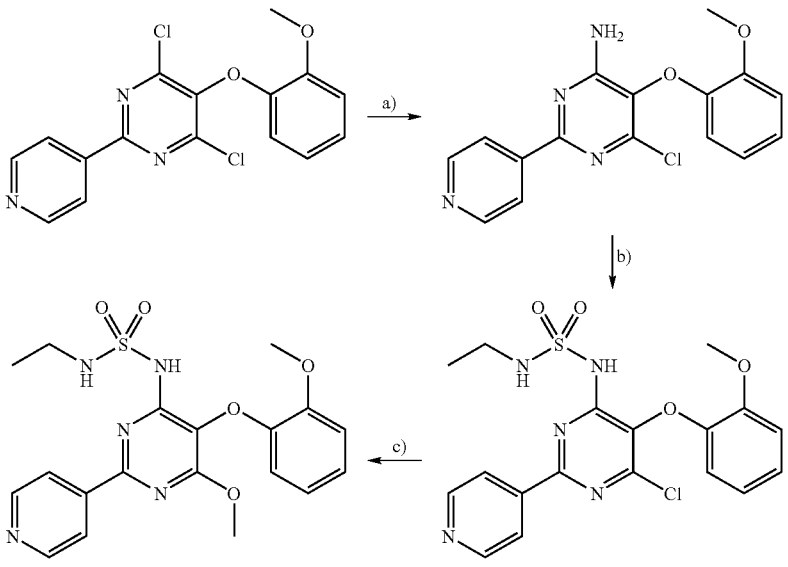


-continued



4-i-Propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (50 mg, Example 3) was dissolved in THF (8 ml). Sodium hydride (12 mg, 60% dispersion in mineral oil) was added and stirring continued for 10 min. 5-Trifluoromethyl-2-chloro-pyridine (28 mg) was added and the mixture was heated to 60° C. for 180 min. The solvents were evaporated, water (12 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off, washed with water and purified by recrystallization with diethylether to give 4-i-propyl-phenyl sulfamic acid-[6-[2-(5-trifluoromethyl-pyridin-2-yloxy)-ethoxy]-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (41 mg). t_R=5.81 min, (LC); $[M+H]^+$=697.17 (ES+).

Example 7

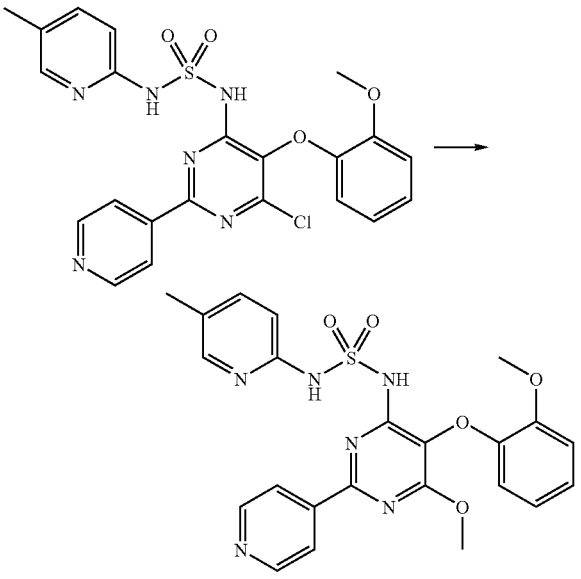


a) 4,6-Dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (2.9 g, Referential Example 1d)) was suspended in dioxane (30 ml) and ammonia (gaseous) was introduced until the solution was saturated. Stirring was continued for 7 days while the saturation of the reaction mixture with ammonia (gaseous) was repeated every 16 to 20 h. The solvent was evaporated, water was added to the residue and the precipitate was filtered off. After drying at HV/50° C. 4-amino-6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (2.7 g) was obtained.

b) 4-Amino-6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (100 mg) was dissolved in THF (5 ml) and DCM (5 ml). DBU (46 mg) and DMAP (37 mg) were added followed by the addition of ethyl-sulfamoylchloride (prepared from ethylamine hydrochloride and sulfuryl chloride). The mixture was stirred for 12 h at r.t. The solvent was evaporated. Water and a 10% solution of citric acid were added followed by extraction with EtOAc and DCM. The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. After purification of the residue by chromatography over silicagel with EtOAc/methanol/ammonia=4:1:0.5, ethyl sulfamic acid-[6-chloro-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (10 mg) was obtained. t_R=4.31 min, (LC); $[M+H]^+$=436.14 (ES+).

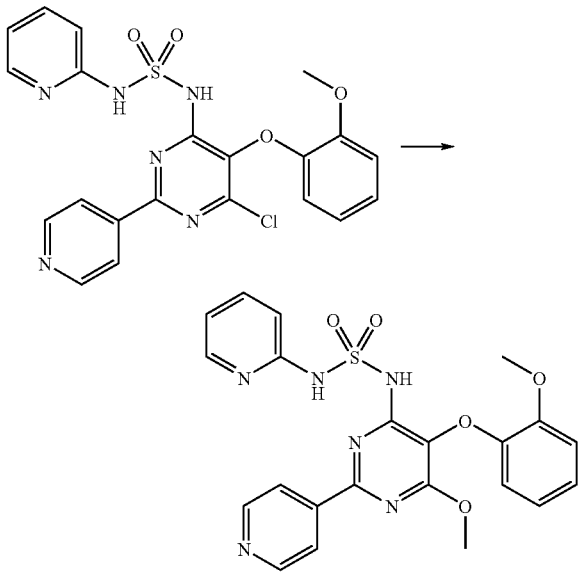
c) Ethyl sulfamic acid-[6-chloro-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (14 mg) was suspended in methanol (1 ml) followed by addition of a solution of potassium tert.-butylate (8.5 mg) in methanol (1 ml). The mixture was heated to 85° C. for 18 h. The solvent was evaporated and water and a 10% solution of citric acid was added. The precipitate was filtered off and washed with water. After drying at HV ethyl sulfamic acid-[6-methoxy-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (10 mg) were obtained. t_R=4.25 min, (LC); $[M+H]^+$=432.32 (ES+).

Example 8



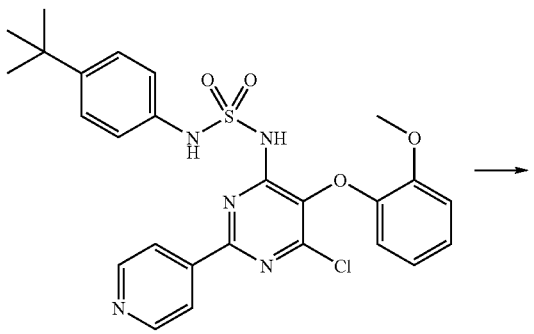
Sodium hydride (100 mg, 60% dispersion in mineral oil) was dissloved in methanol (1.2 ml). 5-methyl-pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (50 mg, Referential Example 11), DMF (0.5 ml) and THF (1 ml) was added and the solution was stirred for 30 h at 80° C. The solvents were evaporated and the residue was washed with hexane (3×) and the hexane was decanted. A solution of 10% citric acid was added and the precipitate was filtered off and washed with water. After drying at HV 5-methyl-pyridine-2-sulfamic acid-[6-methoxy-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (37 mg) was obtained. t_R=3.73 min, (LC); $[M+H]^+$=495.38 (ES+).

Example 9

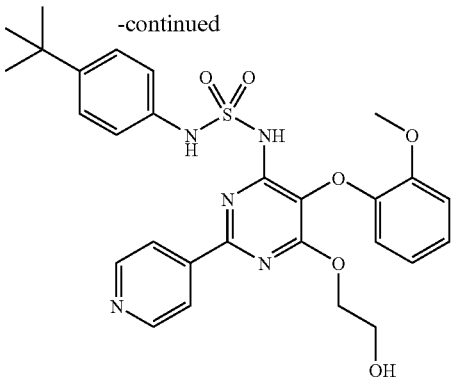


Pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (15 mg, Referential Example 12) was suspended in THF (1 ml) and DMF (0.2 ml) and sodium methylate (40 mg) was added. The mixture was stirred for 90 h at 80° C. followed by evaporation of the solvents. A solution of 10% citiric acid was added to the residue. The precipitate was filtered off and washed with water. After drying at HV pyridine-2-sulfamic acid-[6-methoxy-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (7 mg) was obtained. t_R=3.55 min, (LC); $[M-H]^+$=479.41 (ES−).

Example 10

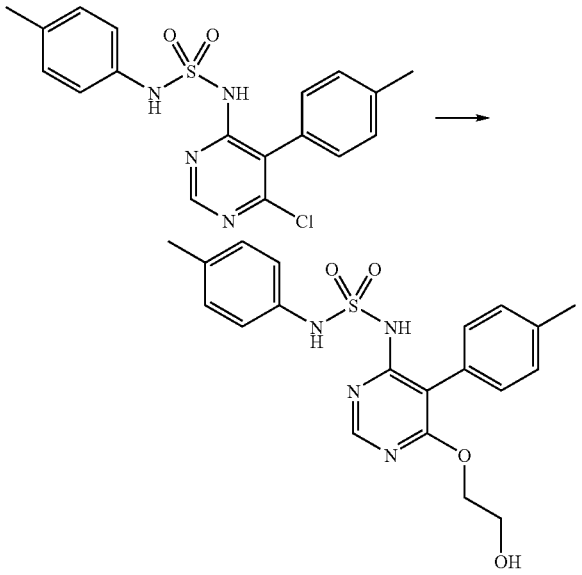


-continued



Sodium hydride (28 mg, 60% dispersion in mineral oil) was dissolved in ethyleneglycol (1.2 ml) and 1,2-dimethoxy-ethane (1 ml). 4-t-butyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (75 mg, Referential Example 10) was added and stirring continued for 90 h at 80° C. The mixture was evaporated and a 10% solution of citric acid was added. The precipitate was filtered off and washed with water. After purification by chromatography over silica gel with EtOAc 4-t-butyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (40 mg) could be isolated. t_R=4.81 min, (LC); $[M+H]^+$=566.35 (ES−).

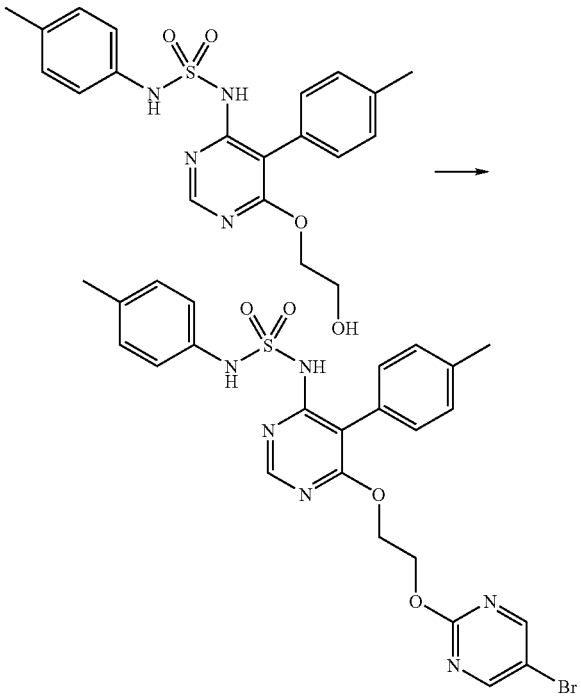
Example 11



To a mixture of 1,2-dimethoxyethan (15 ml) and ethyl-eneglycol (40 ml) was added sodium (298 mg) in small portions. The mixture was stirred until the sodium was completely dissolved. Then DMF (15 ml), followed by 4-methyl-phenyl sulfamic acid-[6-chloro-5-(p-tolyl)-4-pyri-midinyl]-amide (1.0 g, Referential Example 14) was added. Stirring was continued for 4 days at 100° C. The mixture was evaporated and water (150 ml) was added to the residue followed by addition of acetic acid (1.0 ml). The precipitate was filtered off, washed with water and dried. The crude material was purified by chromatography over silicagel with EtOAc/methanol/aquous ammonia (25%)=4/1/0.5 to give

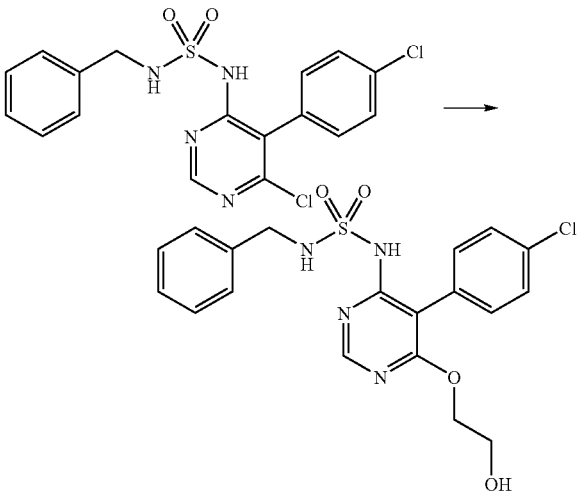
4-methyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(p-tolyl)-4-pyrimidinyl]-amide (500 mg). t_R=4.38 (LC); $[M+H]^+$=415.19 (ES+).

Example 12



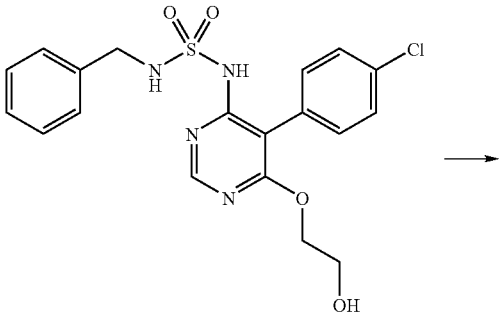
To 4-methyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(p-tolyl)-4-pyrimidinyl]-amide (47 mg, Example 11) dissolved in THF (8 ml) was added sodium hydride (14.6 mg, 60% dispersion in mineral oil) and stirring was contin-ued for 15 min followed by the addition of 5-bromo-2-chloro-pyrimidine (39 mg). Stirring was continued for 2 h at 50° C. and 80 h at r.t. The mixture was evaoprated and a 10% citric acid solution was added. The precipitate was filtered off, washed with water and purified by chromatography over silicagel with EtOAc/Hex=1/1 to give 4-methyl-phenyl sul-famic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(p-tolyl)-4-pyrimidinyl]-amide (34 mg). t_R=5.34 (LC); $[M+H]^+$=573.02 (ES+).

Example 13

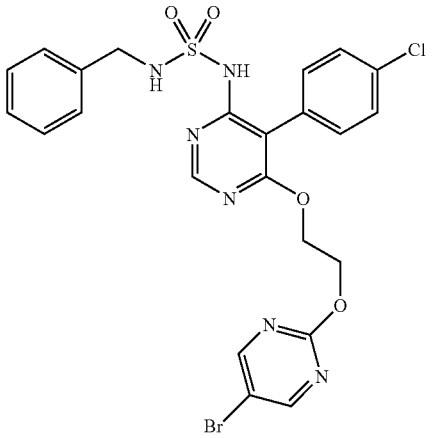


Potassium tert.-butoxide (3.5 g) was dissolved in ethyl-eneglycol (35 ml), benzyl sulfamic acid-[6-chloro-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (1.8 g, Referential Example 15) was added and the mixture was heated to 102° C. for 11 h. The mixture was poured onto ice/water and acidified to pH=4 with solid citric acid. The precipitated product was filtered off, washed with water and dried at HV to give benzyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (1.77 g). t_R=4.36 (LC); $[M+H]^+$=435.09 (ES+).

Example 14



-continued



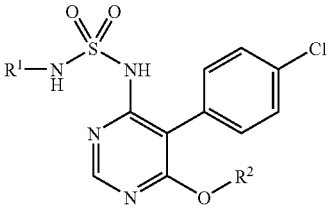
Benzyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (375 mg, Example 13) was dissolved in THF (30 ml) followed by addition of sodium hydride (60/dispersion in mineral oil) (140 mg).

The mixture was stirred for 30 min followed by the addition of 5-bromo-2-chloro-pyrimidine (320 mg). Stirring was continued at 60° C. for 8 h. The reaction mixture was poured onto ice/water and acidified with solid citric acid. The precipitate was filtered off and purified by chromatography over silicagel with hexane/EtOAc=2/1 to give benzyl sulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (198 mg). t_R=5.32 (LC); $[M+H]^+$=592.68 (ES+).

Examples 15–202

The corresponding starting materials are treated in a manner according to the procedures given in examples 1–14 to give the compounds as listed in Tables 3–36.

TABLE 3



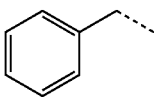
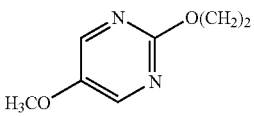
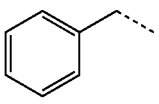
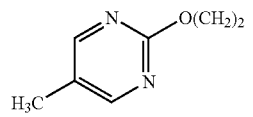
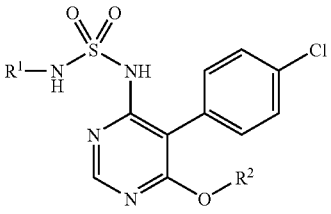
Ex. No.	R^1	R^2	LC-MS
15			t_R = 5.00 $[M + H]^+$: 543.18
16			t_R = 4.95 $[M + H]^+$: 527.28

TABLE 3-continued



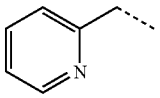
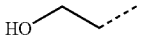
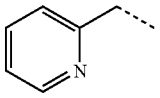
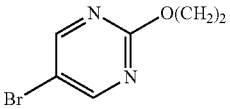
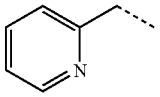
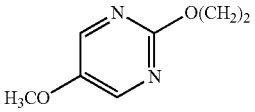
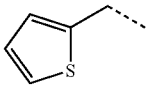
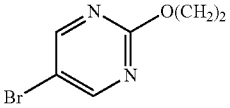
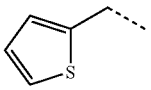
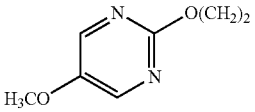
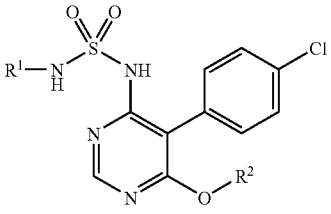
Ex. No.	R^1	R^2	LC-MS
17			t_R = 3.28 $[M + H]^+$: 435.65
18			t_R = 4.46 $[M + H]^+$: 594.25
19			t_R = 4.03 $[M + H]^+$: 544.10
20			t_R = 5.21 $[M + H]^+$: 599.20
21			t_R = 4.84 $[M + H]^+$: 548.97

TABLE 4



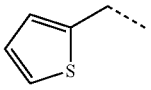
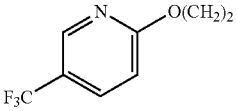
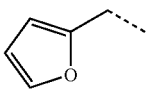
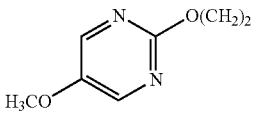
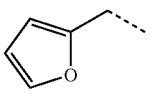
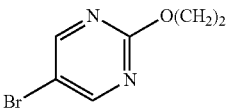
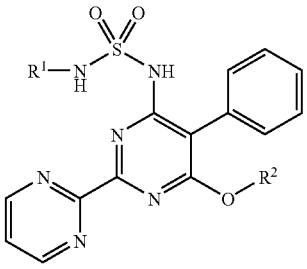
Ex. No.	R^1	R^2	LC-MS
22			t_R = 5.67 $[M + H]^+$: 585.75
23			t_R = 4.67 $[M + H]^+$: 532.77
24			t_R = 5.07 $[M + H]^+$: 582.71

TABLE 5



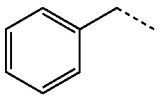
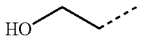
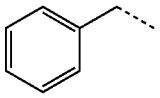
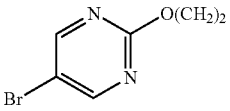
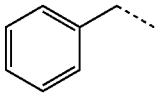
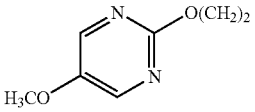
Ex. No.	R^1	R^2	LC-MS
25			t_R = 4.07 $[M + H]^+$: 479.11
26			t_R = 4.88 $[M + H]^+$: 637.54
27			t_R = 4.51 $[M - H]^+$: 584.93

TABLE 6

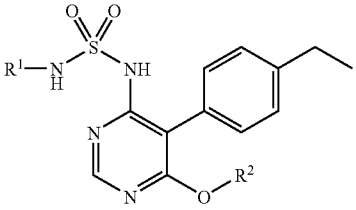
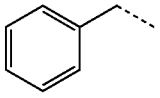
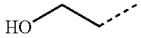
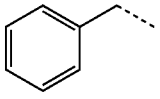
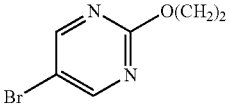
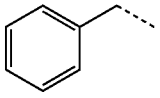
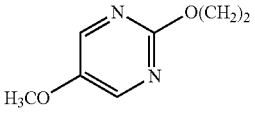
Ex. No.	R^1	R^2	LC-MS
			
28			t_R = 4.52 $[M + H]^+$: 429.14
29			t_R = 5.48 $[M + H]^+$: 585.38
30			t_R = 5.12 $[M + H]^+$: 537.22

TABLE 6-continued

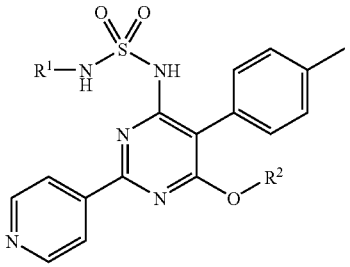
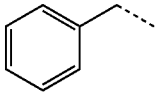
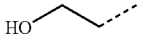
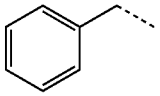
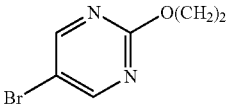
Ex. No.	R^1	R^2	LC-MS
			
31			t_R = 3.99 $[M + H]^+$: 492.23
32			t_R = 5.04 $[M + H]^+$: 650.50

TABLE 7

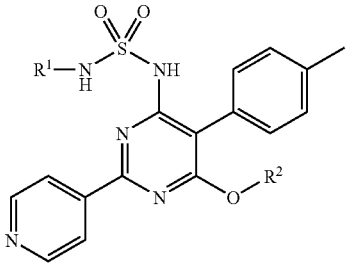
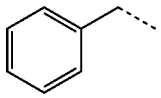
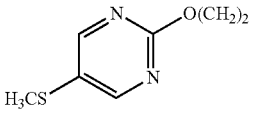
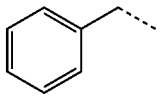
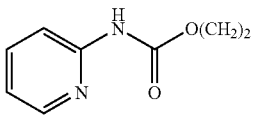
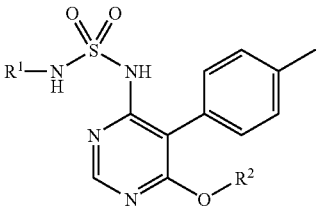
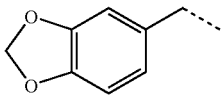
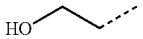
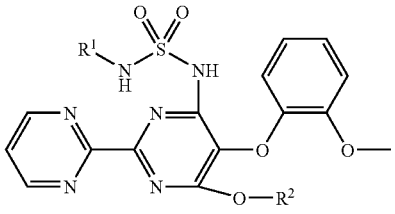
Ex. No.	R^1	R^2	LC-MS
			
33			t_R = 5.00 $[M + H]^+$: 616.18
34			t_R = 4.47 $[M + H]^+$: 612.41
			
35			t_R = 4.27 $[M + H]^+$: 459.15

TABLE 8



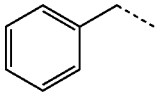
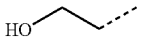
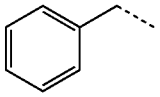
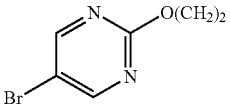
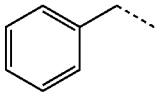
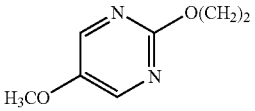
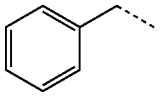
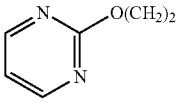
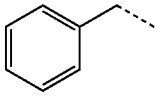
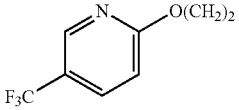
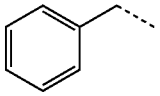
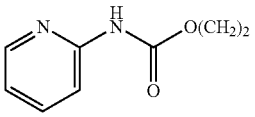
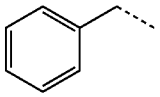
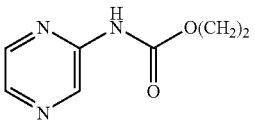
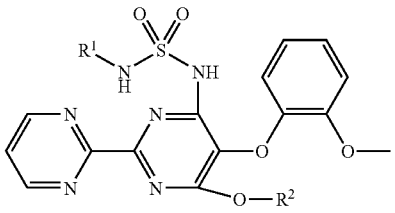
Ex. No.	R^1	R^2	LC-MS
36			t_R = 4.13 $[M + H]^+$: 525.17
37			t_R = 4.87 $[M + H]^+$: 682.50
38			t_R = 4.55 $[M + H]^+$: 631.05
39			t_R = 4.38 $[M + H]^+$: 603.45
40			t_R = 5.31 $[M + H]^+$: 670.27
41			t_R = 4.36 $[M + H]^+$: 645.11
42			t_R = 4.29 $[M + H]^+$: 646.12

TABLE 9



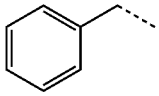
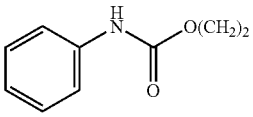
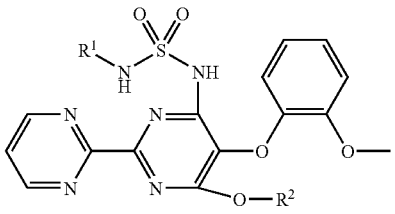
Ex. No.	R^1	R^2	LC-MS
43			t_R = 4.89 $[M + H]^+$: 644.24

TABLE 9-continued



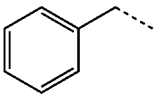
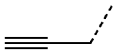
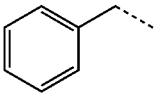
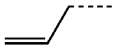
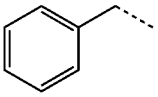
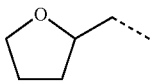
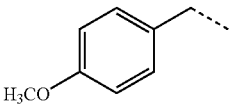
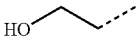
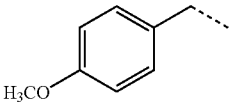
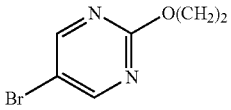
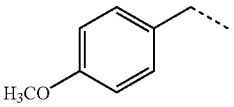
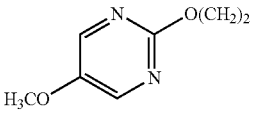
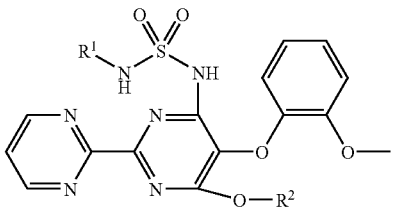
Ex. No.	R^1	R^2	LC-MS
44			t_R = 4.60 $[M + H]^+$: 519.18
45			t_R = 4.74 $[M + H]^+$: 521.21
46			t_R = 4.71 $[M + H]^+$: 565.66
47			t_R = 4.10 $[M + H]^+$: 555.59
48			t_R = 4.82 $[M + H]^+$: 713.18
49			t_R = 4.52 $[M + H]^+$: 663.54

TABLE 10



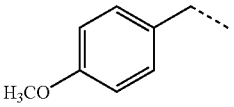
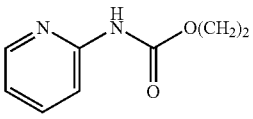
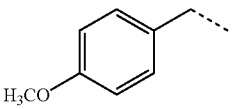
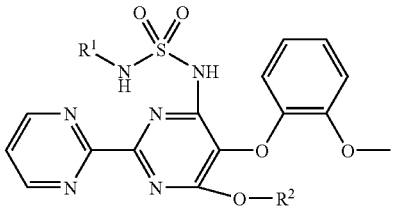
Ex. No.	R^1	R^2	LC-MS
50			t_R = 4.32 $[M + H]^+$: 675.34
51			t_R = 4.51 $[M + H]^+$: 524.91

TABLE 10-continued



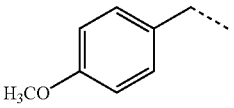
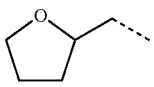
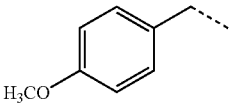
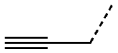
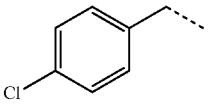
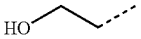
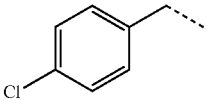
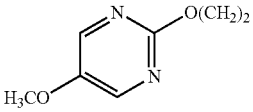
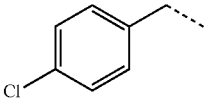
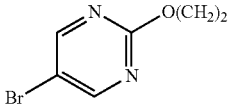
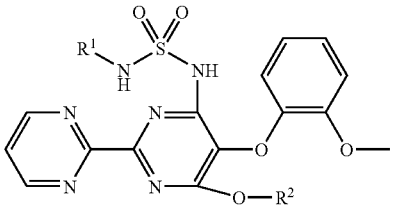
Ex. No.	R^1	R^2	LC-MS
52			t_R = 4.67 $[M + H]^+$: 595.20
53			t_R = 4.65 $[M + H]^+$: 549.33
54			t_R = 4.35 $[M + H]^+$: 559.30
55			t_R = 4.79 $[M + H]^+$: 667.34
56			t_R = 5.11 $[M + H]^+$: 717.09

TABLE 11



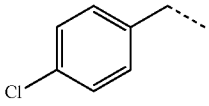
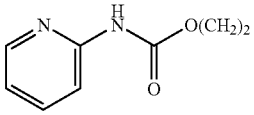
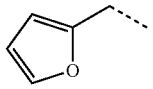
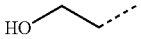
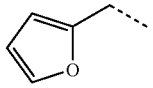
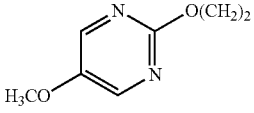
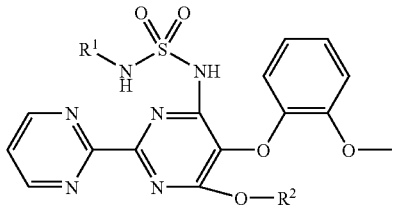
Ex. No.	R^1	R^2	LC-MS
57			t_R = 4.71 $[M - H]^+$: 678.68
58			t_R = 3.93 $[M + H]^+$: 515.38
59			t_R = 4.46 $[M + H]^+$: 623.48

TABLE 11-continued



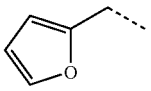
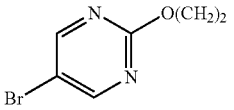
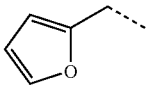
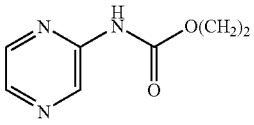
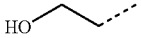
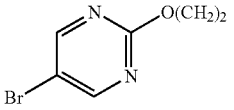
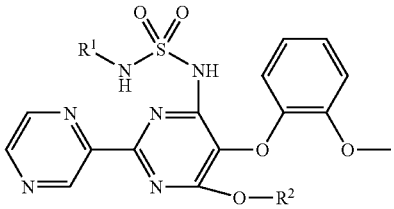
Ex. No.	R^1	R^2	LC-MS
60			t_R = 4.75 $[M + H]^+$: 673.39
61			t_R = 4.15 $[M + H]^+$: 636.34
183			t_R = 3.72 $[M + H]^+$: 462.98
184			t_R = 4.54 $[M + H]^+$: 619.06

TABLE 12



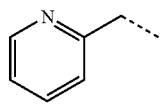
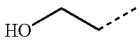
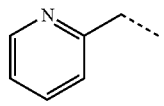
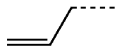
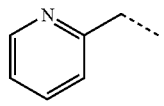
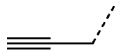
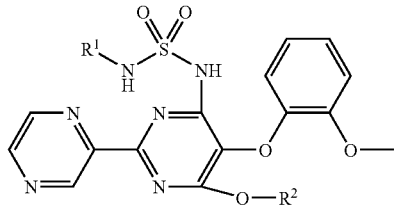
Ex. No.	R^1	R^2	LC-MS
62			t_R = 3.38 $[M + H]^+$: 526.04
63			t_R = 4.29 $[M + H]^+$: 521.79
64			t_R = 4.10 $[M + H]^+$: 520.10

TABLE 12-continued



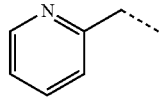
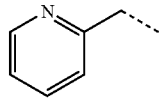
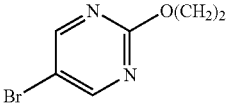
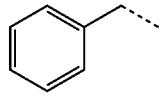
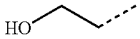
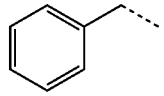
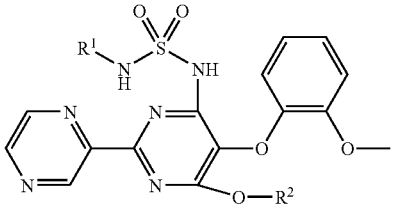
Ex. No.	R^1	R^2	LC-MS
65			t_R = 3.87 $[M + H]^+$: 496.09
66			t_R = 4.40 $[M + H]^+$: 683.15
67			t_R = 4.30 $[M + H]^+$: 525.25
68			t_R = 4.84 $[M - H]^+$: 493.13

TABLE 13



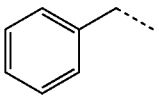
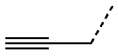
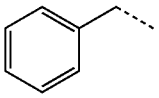
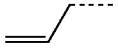
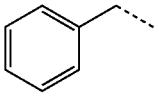
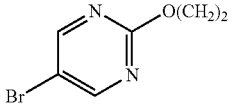
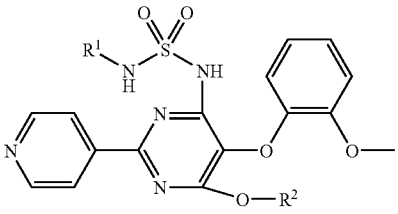
Ex. No.	R^1	R^2	LC-MS
69			t_R = 4.95 $[M - H]^+$: 517.58
70			t_R = 5.13 $[M + H]^+$: 521.30
71			t_R = 5.22 $[M + H]^+$: 683.42

TABLE 14



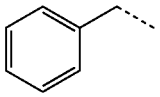
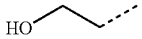
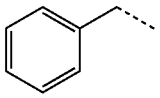
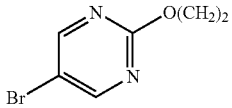
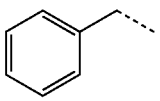
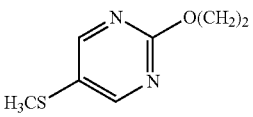
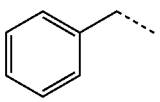
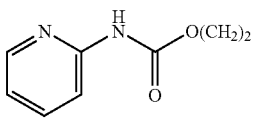
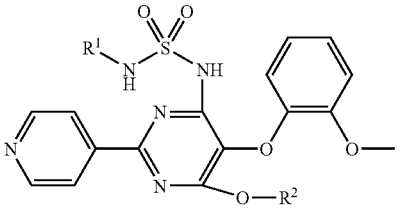
Ex. No.	R^1	R^2	LC-MS
72			t_R = 3.79 $[M + H]^+$: 524.28
73			t_R = 4.76 $[M + H]^+$: 681.59
74			t_R = 4.70 $[M + H]^+$: 648.25
75			t_R = 4.30 $[M + H]^+$: 645.65

TABLE 14-continued



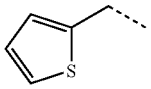
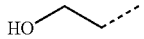
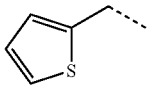
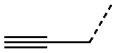
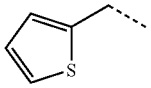
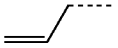
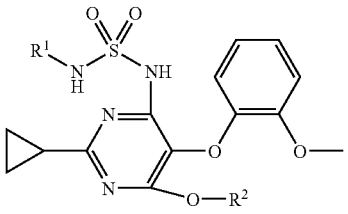
Ex. No.	R^1	R^2	LC-MS
76			t_R = 3.73 $[M + H]^+$: 530.25
77			t_R = 4.38 $[M + H]^+$: 524.23
78			t_R = 4.59 $[M + H]^+$: 526.10

TABLE 16



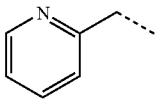
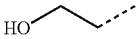
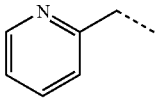
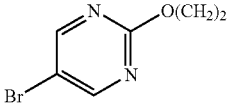
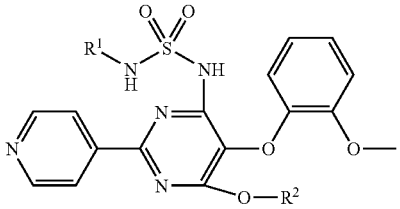
Ex. No.	R^1	R^2	LC-MS
83			t_R = 3.38 $[M + H]^+$: 488.30
84			t_R = 4.46 $[M + H]^+$: 646.17

TABLE 15



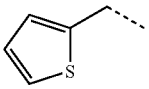
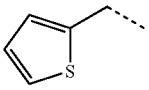
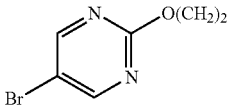
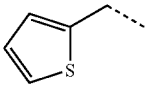
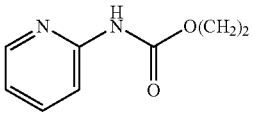
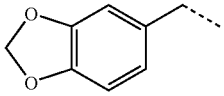
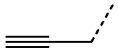
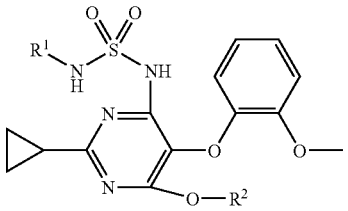
Ex. No.	R^1	R^2	LC-MS
79			t_R = 4.36 $[M + H]^+$: 500.14
80			t_R = 4.82 $[M + H]^+$: 688.54
81			t_R = 4.25 $[M + H]^+$: 650.09
82			t_R = 4.43 $[M + H]^+$: 562.16

TABLE 16-continued



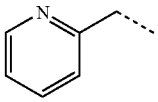
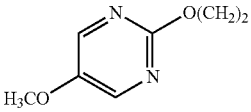
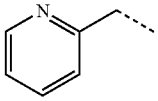
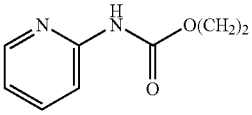
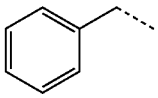
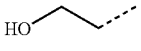
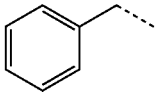
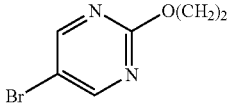
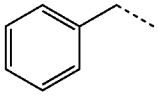
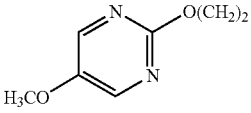
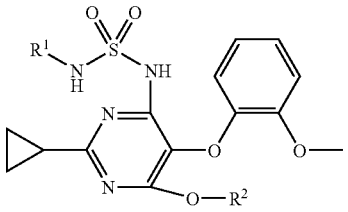
Ex. No.	R^1	R^2	LC-MS
85			t_R = 4.15 [M + H]$^+$: 596.31
86			t_R = 3.96 [M + H]$^+$: 608.69
87			t_R = 4.77 [M + H]$^+$: 488.18
88			t_R = 5.89 [M + H]$^+$: 644.83
89			t_R = 5.56 [M + H]$^+$: 595.20

TABLE 17



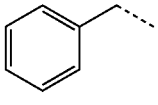
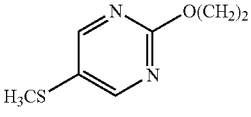
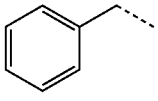
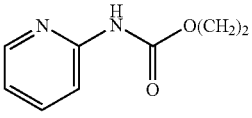
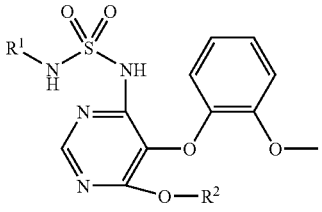
Ex. No.	R^1	R^2	LC-MS
90			t_R = 5.82 [M + H]$^+$: 611.19
91			t_R = 5.31 [M + H]$^+$: 607.32

TABLE 18



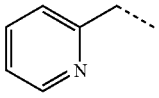
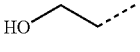
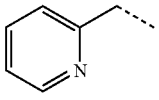
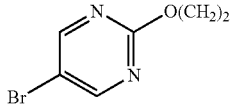
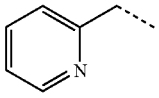
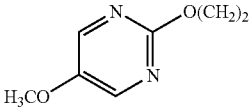
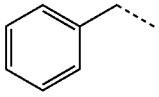
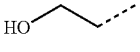
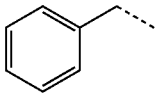
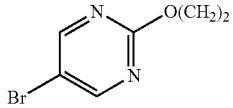
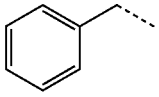
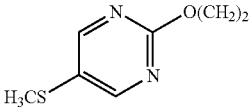
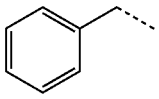
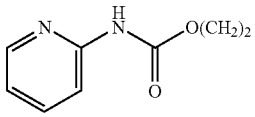
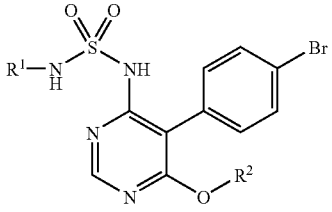
Ex. No.	R^1	R^2	LC-MS
92			t_R = 2.54 [M + H]$^+$: 448.08
93			t_R = 4.20 [M + H]$^+$: 605.54
94			t_R = 3.82 [M + H]$^+$: 556.15
95			t_R = 4.14 [M + H]$^+$: 447.26
96			t_R = 5.10 [M + H]$^+$: 604.67
97			t_R = 5.01 [M + H]$^+$: 571.16
98			t_R = 4.53 [M + H]$^+$: 567.23

TABLE 19



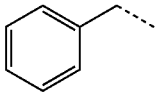
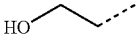
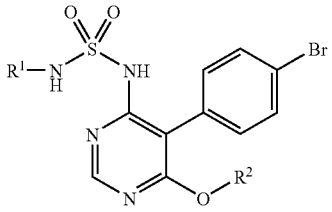
Ex. No.	R^1	R^2	LC-MS
99			t_R = 4.46 [M + H]$^+$: 481.20

TABLE 19-continued



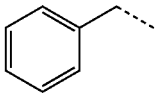
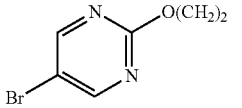
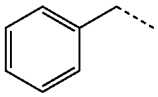
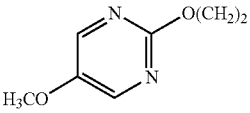
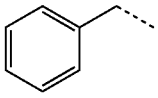
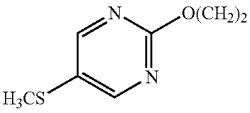
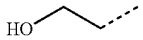
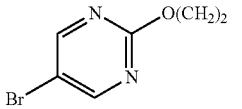
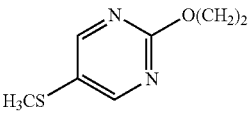
Ex. No.	R^1	R^2	LC-MS
100			t_R = 5.55 [M + H]$^+$: 637.07
101			t_R = 5.14 [M + H]$^+$: 589.15
102			t_R = 5.55 [M + H]$^+$: 603.27
103			t_R = 3.88 [M + H]$^+$: 419.01
104			t_R = 4.93 [M + H]$^+$: 575.13
105			t_R = 4.84 [M + H]$^+$: 543.20

TABLE 20

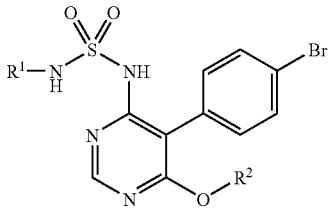
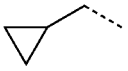
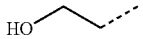
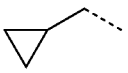
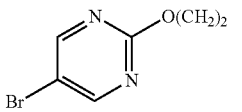
Ex. No.	R^1	R^2	LC-MS
			
106			t_R = 4.12 [M + H]$^+$: 445.11
107			t_R = 5.03 [M + H]$^+$: 601.28

TABLE 20-continued

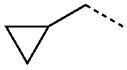
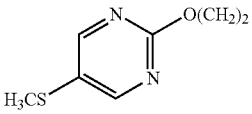
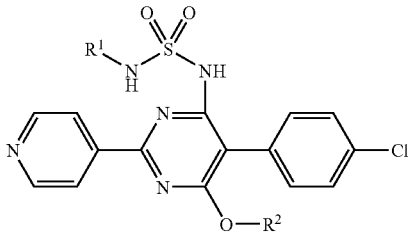
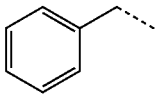
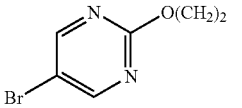
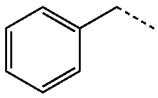
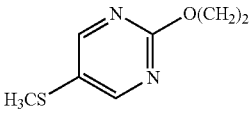
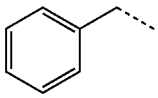
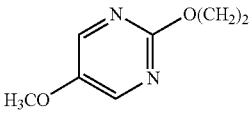
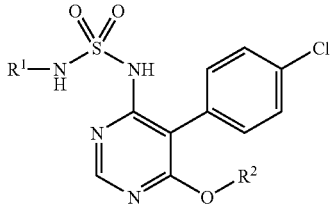
Ex. No.	R^1	R^2	LC-MS
108			t_R = 4.98 [M + H]$^+$: 568.44
			
109			t_R = 4.92 [M + H]$^+$: 670.30
110			t_R = 5.07 [M + H]$^+$: 636.34
111			t_R = 4.76 [M + H]$^+$: 620.07

TABLE 21



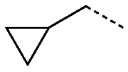
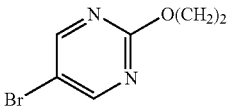
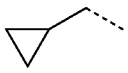
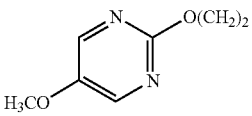
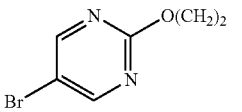
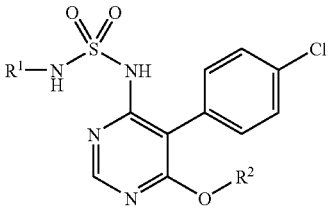
Ex. No.	R^1	R^2	LC-MS
112			t_R = 5.28 [M + H]$^+$: 557.18
113			t_R = 4.86 [M + H]$^+$: 507.28
114			t_R = 4.92 [M + H]$^+$: 543.16

TABLE 21-continued



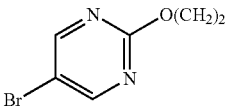
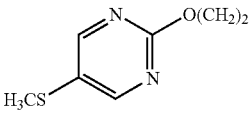
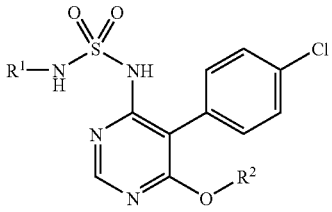
Ex. No.	R^1	R^2	LC-MS
115			t_R = 4.87 $[M + H]^+$: 531.13
116			t_R = 4.78 $[M + H]^+$: 497.24

TABLE 21-continued



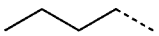
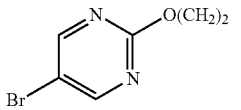
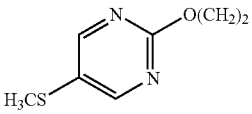
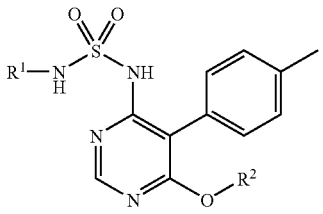
Ex. No.	R^1	R^2	LC-MS
117			t_R = 5.32 $[M + H]^+$: 559.19
118			t_R = 5.23 $[M + H]^+$: 525.31

TABLE 22



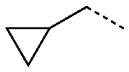
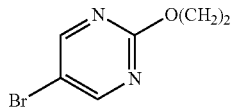
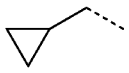
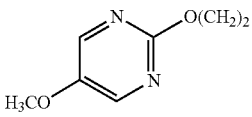
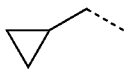
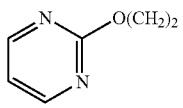
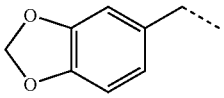
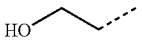
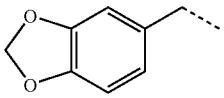
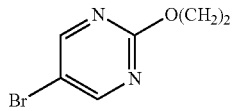
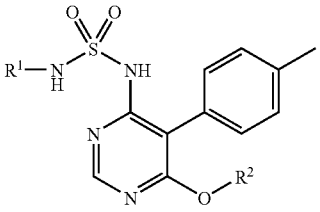
Ex. No.	R^1	R^2	LC-MS
119			t_R = 5.20 $[M + H]^+$: 537.14
120			t_R = 4.77 $[M + H]^+$: 487.25
121			t_R = 4.56 $[M + H]^+$: 456.89
144			t_R = 4.27 $[M + H]^+$: 459.15
145			t_R = 5.77 $[M + H]^+$: 616.66

TABLE 22-continued



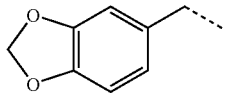
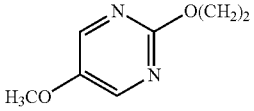
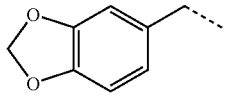
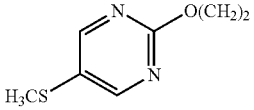
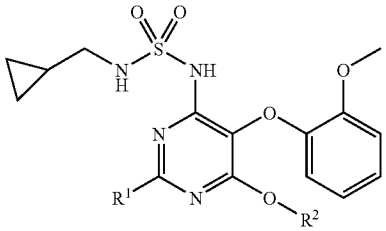
Ex. No.	R^1	R^2	LC-MS
146			t_R = 6.01 $[M + H]^+$: 567.36
147			t_R = 5.22 $[M + H]^+$: 582.88

TABLE 23



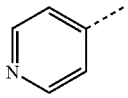
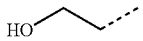
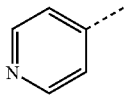
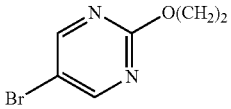
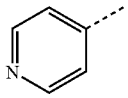
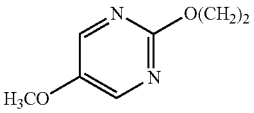
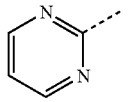
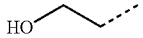
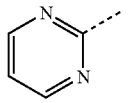
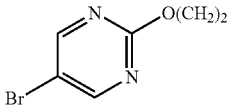
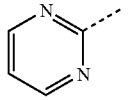
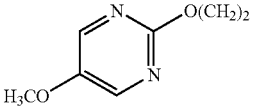
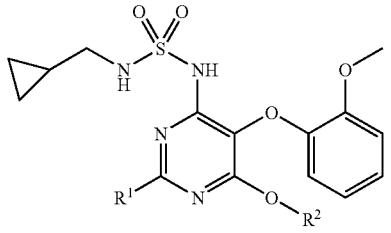
Ex. No.	R^1	R^2	LC-MS
122			t_R = 3.63 $[M + H]^+$: 488.49
123			t_R = 4.66 $[M + H]^+$: 646.30
124			t_R = 4.29 $[M + H]^+$: 596.44
125			t_R = 3.96 $[M + H]^+$: 489.56
126			t_R = 4.79 $[M + H]^+$: 645.07
127			t_R = 4.47 $[M + H]^+$: 597.31

TABLE 23-continued



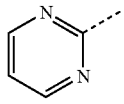
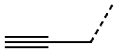
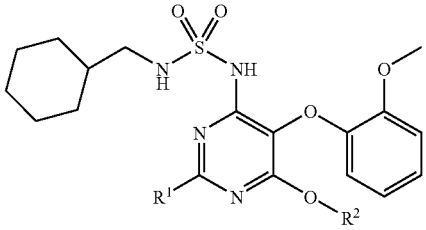
Ex. No.	R^1	R^2	LC-MS
128			t_R = 4.47 $[M + H]^+$: 483.34

TABLE 24



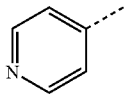
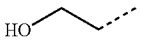
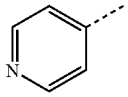
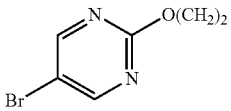
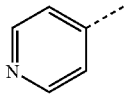
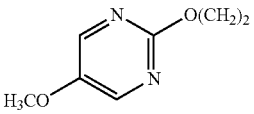
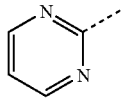
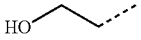
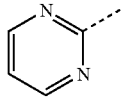
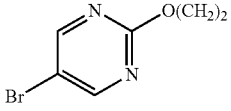
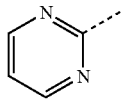
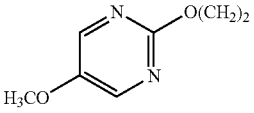
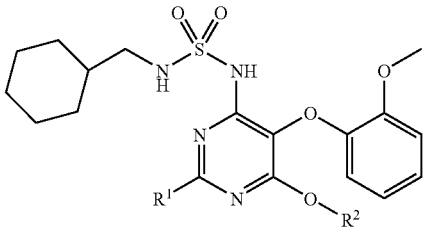
Ex. No.	R^1	R^2	LC-MS
129			t_R = 4.29 $[M + H]^+$: 530.49
130			t_R = 5.35 $[M + H]^+$: 688.27
131			t_R = 4.93 $[M + H]^+$: 638.64
132			t_R = 4.70 $[M + H]^+$: 531.54
133			t_R = 5.39 $[M + H]^+$: 689.26
134			t_R = 5.06 $[M + H]^+$: 639.36

TABLE 24-continued



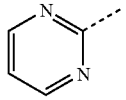
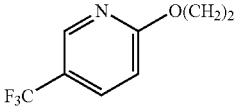
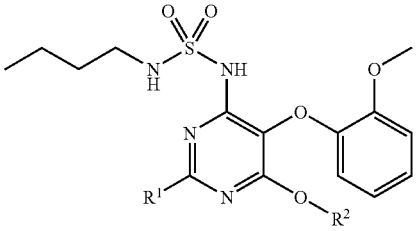
Ex. No.	R^1	R^2	LC-MS
135			t_R = 5.83 $[M + H]^+$: 676.34

TABLE 25



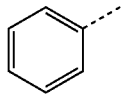
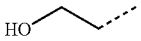
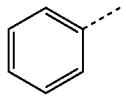
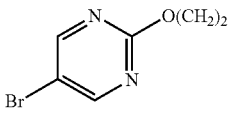
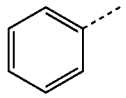
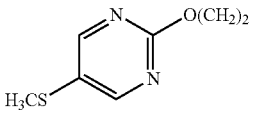
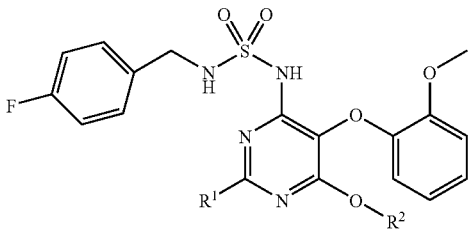
Ex. No.	R^1	R^2	LC-MS
136			t_R = 4.11 $[M + H]^+$: 491.29
137			t_R = 4.88 $[M + H]^+$: 649.18
138			t_R = 4.82 $[M + H]^+$: 615.67

TABLE 26



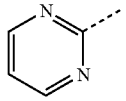
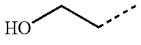
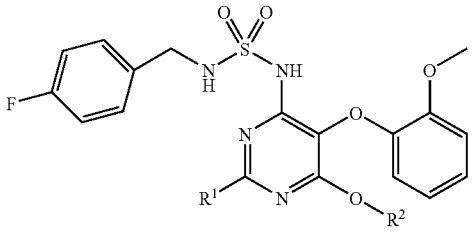
Ex. No.	R^1	R^2	LC-MS
139			t_R = 4.27 $[M + H]^+$: 543.37

TABLE 26-continued



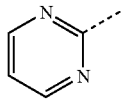
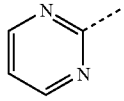
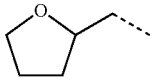
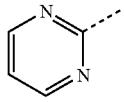
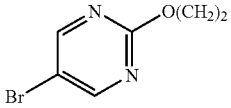
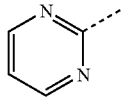
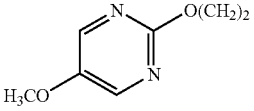
Ex. No.	R^1	R^2	LC-MS
140		H_3C----	t_R = 4.55 $[M + H]^+$: 513.31
141			t_R = 4.70 $[M + H]^+$: 583.52
142			t_R = 4.92 $[M + H]^+$: 701.37
143			t_R = 4.60 $[M + H]^+$: 651.40

TABLE 27

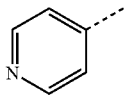
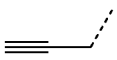
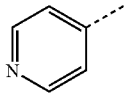
Ex. No.	R^1	R^2	LC-MS
148			t_R = 4.43 $[M + H]^+$: 562.16
149		H_3C----	t_R = 4.27 $[M + H]^+$: 538.18

TABLE 27-continued

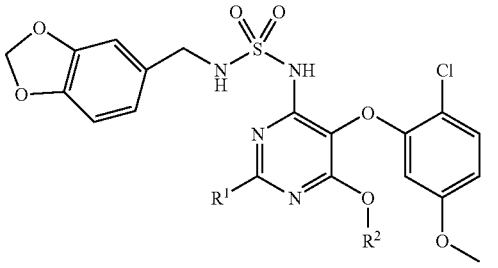
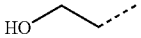
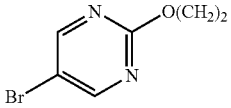
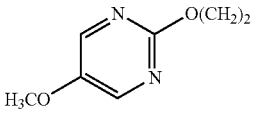
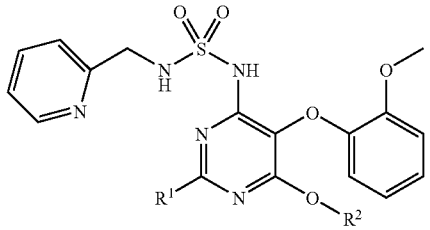
Ex. No.	R^1	R^2	LC-MS
			
150			t_R = 4.37 $[M - H]^+$: 522.83
151			t_R = 5.21 $[M + H]^+$: 682.98
152			t_R = 4.86 $[M - H]^+$: 631.19

TABLE 28



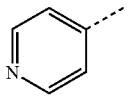
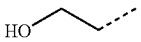
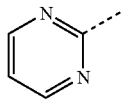
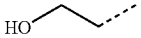
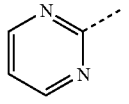
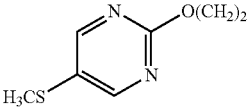
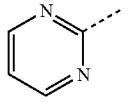
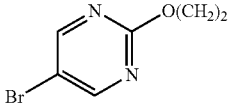
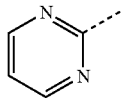
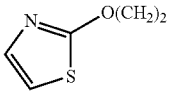
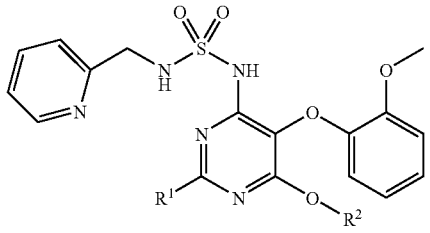
Ex. No.	R^1	R^2	LC-MS
153			t_R = 3.15 $[M - H]^+$: 523.09
154			t_R = 3.20 $[M + H]^+$: 526.44
155			t_R = 3.96 $[M + H]^+$: 650.39
156			t_R = 4.00 $[M + H]^+$: 684.29
157			t_R = 3.86 $[M + H]^+$: 609.32

TABLE 28-continued



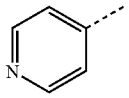
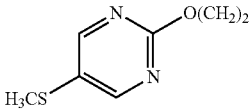
Ex. No.	R^1	R^2	LC-MS
158			t_R = 4.14 $[M + H]^+$: 649.30

TABLE 29

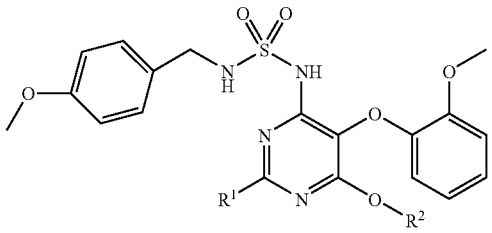
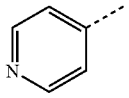
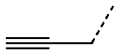
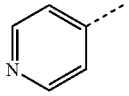
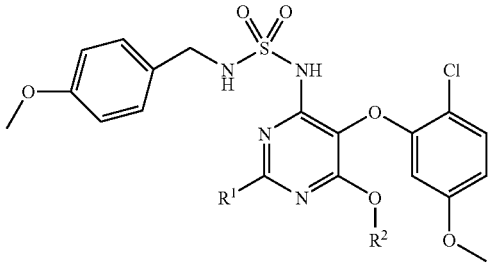
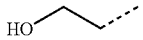
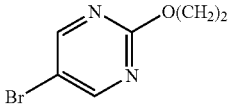
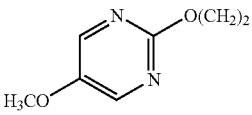
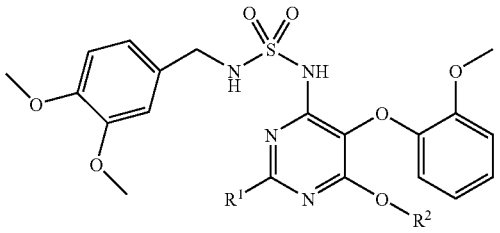
Ex. No.	R^1	R^2	LC-MS
			
160			t_R = 4.58 $[M + H]^+$: 548.41
161			t_R = 4.32 $[M + H]^+$: 524.19
			
162			t_R = 4.41 $[M + H]^+$: 511.11
163			t_R = 5.26 $[M + H]^+$: 668.91
164			t_R = 4.98 $[M + H]^+$: 619.17

TABLE 30



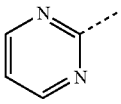
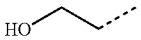
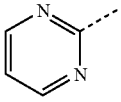
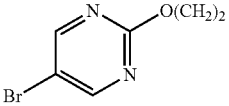
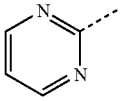
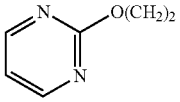
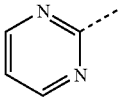
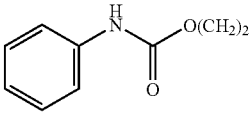
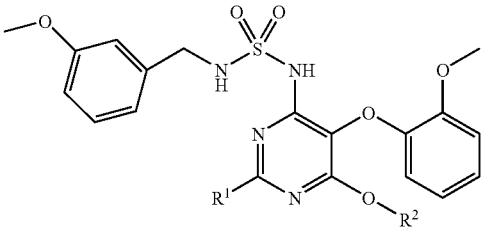
Ex. No.	R^1	R^2	LC-MS
165			t_R = 3.90 $[M + H]^+$: 585.52
166			t_R = 4.69 $[M + H]^+$: 743.19
167			t_R = 4.24 $[M + H]^+$: 663.47
168			t_R = 4.78 $[M + H]^+$: 704.54

TABLE 31



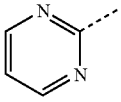
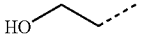
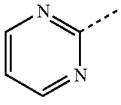
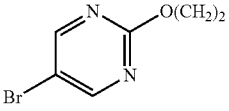
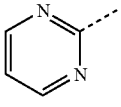
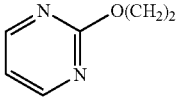
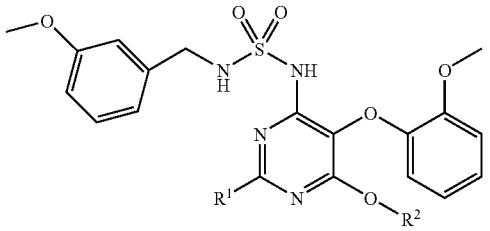
Ex. No.	R^1	R^2	LC-MS
169			t_R = 4.16 $[M + H]^+$: 555.69
170			t_R = 4.76 $[M + H]^+$: 713.26
171			t_R = 4.45 $[M + H]^+$: 633.64

TABLE 31-continued



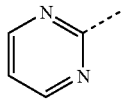
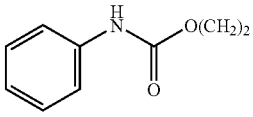
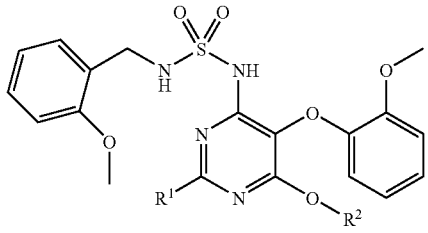
Ex. No.	R^1	R^2	LC-MS
172			t_R = 4.98 $[M + H]^+$: 674.55

TABLE 32



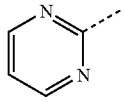
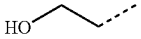
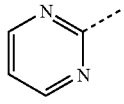
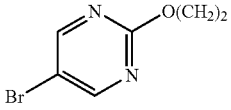
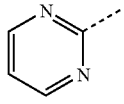
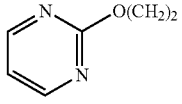
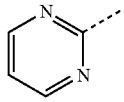
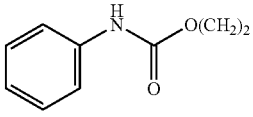
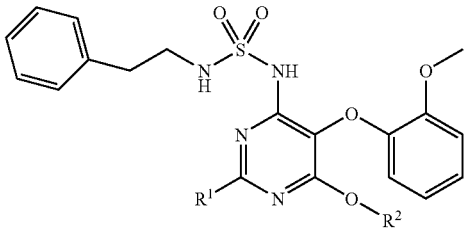
Ex. No.	R^1	R^2	LC-MS
173			t_R = 4.20 $[M + H]^+$: 555.37
174			t_R = 4.99 $[M + H]^+$: 713.35
175			t_R = 4.45 $[M + H]^+$: 633.70
176			t_R = 4.99 $[M + H]^+$: 674.95

TABLE 33



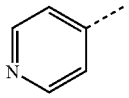
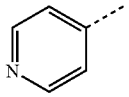
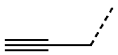
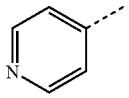
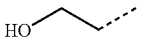
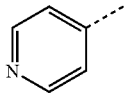
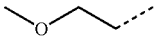
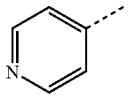
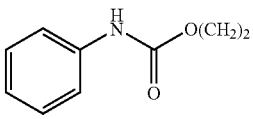
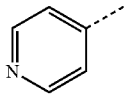
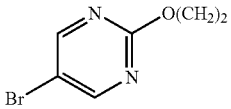
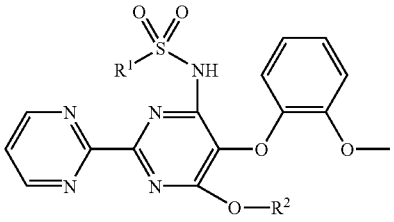
Ex. No.	R^1	R^2	LC-MS
177			t_R = 4.54 $[M + H]^+$: 508.22
178			t_R = 4.62 $[M + H]^+$: 532.23
179			t_R = 3.90 $[M + H]^+$: 538.33
180			t_R = 4.46 $[M + H]^+$: 552.27
181			t_R = 4.78 $[M + H]^+$: 657.46
182			t_R = 4.91 $[M + H]^+$: 696.51

TABLE 34



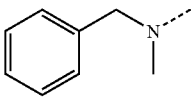
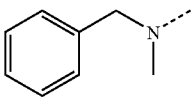
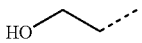
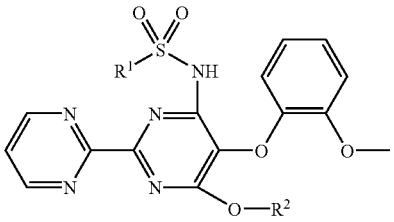
Ex. No.	R^1	R^2	IC-MS
185			t_R = 4.84 $[M - H]^+$: 507.15
186			t_R = 4.51 $[M + H]^+$: 539.47

TABLE 34-continued



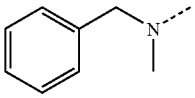
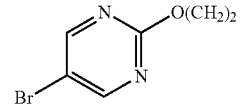
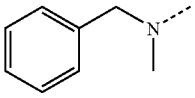
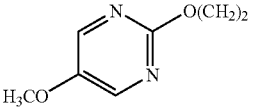
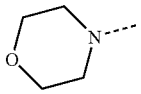
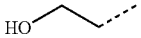
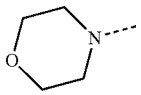
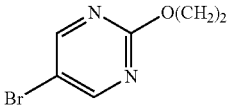
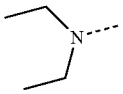
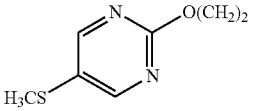
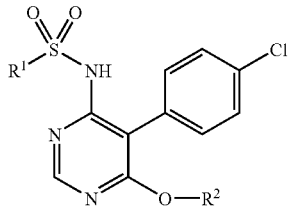
Ex. No.	R^1	R^2	IC-MS
187			t_R = 5.18 $[M - H]^+$: 695.09
188			t_R = 4.86 $[M + H]^+$: 647.43
189			t_R = 3.56 $[M + H]^+$: 505.35
190			t_R = 4.38 $[M + H]^+$: 663.05
191			t_R = 4.77 $[M + H]^+$: 615.32

TABLE 35



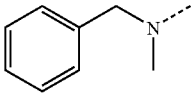
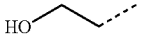
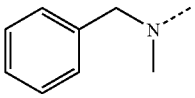
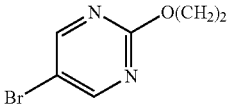
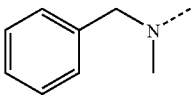
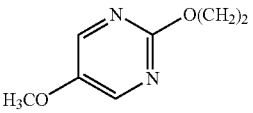
Ex. No.	R^1	R^2	LC-MS
192			t_R = 4.84 $[M - H]^+$: 447.17
193			t_R = 5.66 $[M + H]^+$: 607.22
194			t_R = 5.31 $[M +]H]^+$: 557.42

TABLE 35-continued

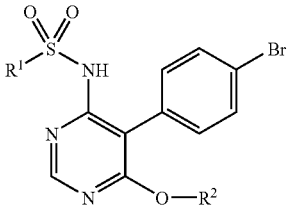
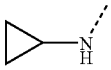
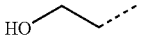
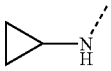
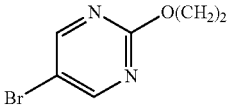
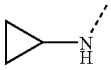
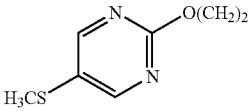
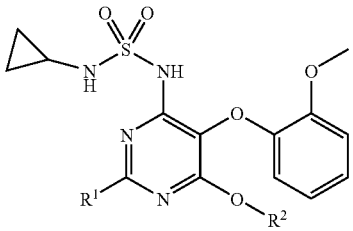
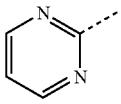
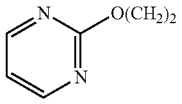
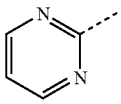
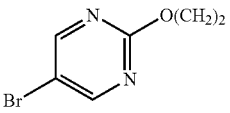
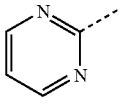
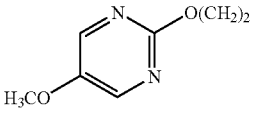
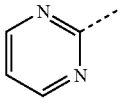
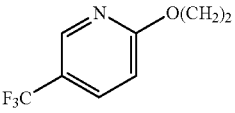
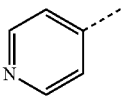
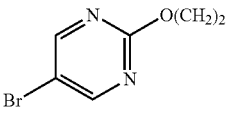
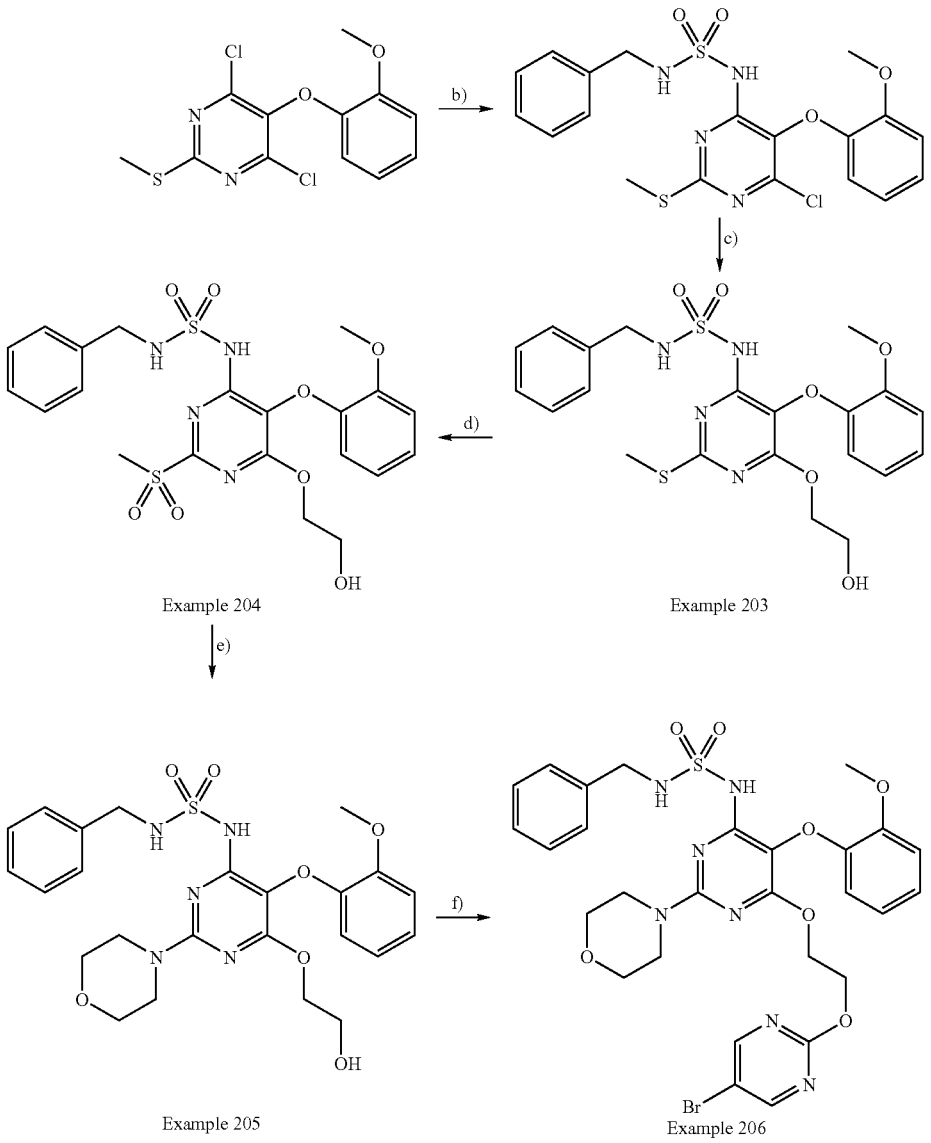
Ex. No.	R^1	R^2	LC-MS
			
195			t_R = 3.92 $[M + H]^+$: 431.09
196			t_R = 4.99 $[M + H]^+$: 587.13
197			t_R = 4.90 $[M + H]^+$: 555.18

TABLE 36



Ex. No.	R^1	R^2	LC-MS
198			t_R = 4.11 $[M + H]^+$: 551.34
199			t_R = 4.61 $[M + H]^+$: 633.37
200			t_R = 4.35 $[M + H]^+$: 583.40
201			t_R = 5.05 $[M + H]^+$: 617.98
202			t_R = 4.51 $[M + H]^+$: 632.16



a) According to the procedures described in [5], the preparation of 4,6-dichloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidine was achieved by the condensation of thiourea (6.4 g) with 2-(2-methoxy-phenoxy)-malonic acid dimethyl ester (20.32 g) followed by reacting the 2-mercapto-5-(2-methoxy-phenoxy)-pyrimidine-4,6-diol with methyliodide (5.9 ml) and subsequent chlorination with phosphorus oxychloride/N,N-dimethylaniline. Yield: 18.6 g; LC-MS: t_R=5.73; $[M+H]^+$=318.2.

b) 4,6-Dichloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidine (1.5 g) was dissolved in DMSO (30 ml) and benzylsulfamic acid amide potassium salt (2.12 g, Referential Example 22) was added. Stirring was continued for 18 h. The reaction mixture was poured onto water, acidified by solid citric acid (1.9 g), cooled to 0° C. and the precipitate was filtered off and purified by column chromatography over silica gel with hexane/EtOAc=2/1 to give benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (1.75 g) as a white powder. LC-MS: t_R=5.27; $[M+H]^+$=467.04.

c) Benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (1.75 g) was added to a solution of potassium tert.-butylate (1.87 g) in ethylene glycol (30 ml) and stirred at 100° C. for 40 h. The reaction mixture was poured onto water (120 ml), acidified with solid citric acid (1.9 g) and cooled to 0° C. The precipitate was filtered off, washed with water and dried at HV to give benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (Example 203). LC-MS: t_R=4.70; $[M+H]^+$=493.09.

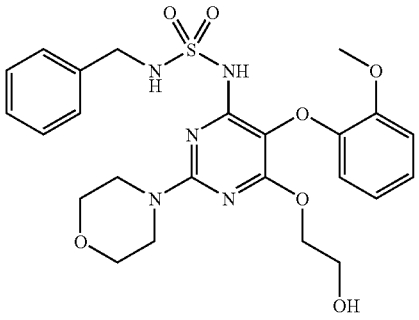
d) Benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (1.49 g) was dissolved in DCM (50 ml) and cooled to 0° C. followed by slow addition of m-chloroperbenzoic acid (1.65 g; 70%) dissolved in DCM (15 ml). Stirring was

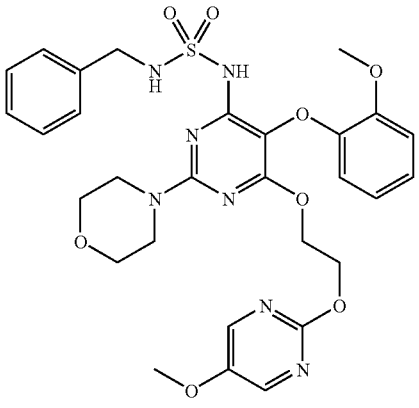
continued for 30 min at 0° C. and for 1.5 h at rt. The mixture was concentrated in vacuo until the product started to precipitate. The product was filtered off and purified by chromatography through silicagel with EtOAc/hexane 2:1 to give benzasulfamic acid [6-(2-hydroxy-ethoxy)-2-methanesulfonyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (Example 204) (1.4 g) as a white powder. LC-MS: t_R=4.12; $[M+H]^+$=525.09.

e) Benzylsulfamic acid [6-(2-hydroxy-ethoxy)-2-methanesulfonyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (85 mg) were dissolved in THF (2 ml) and morpholine (2 ml) was added. The reaction mixture was stirred at 45° C. for 48 hours, poured onto water, acidified with solid citric acid and extracted with EtOAc (2×). The combined EtOAc layers were washed with 10% citric acid solution and with brine, dried over magnesium sulfate, filtered and the solvent was evaporated. The crude product was purified by chromatography on plates with toluene/EtOAc=1/1 to give benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl]-amide (Example 205) (60 mg). LC-MS: t_R=4.69; $[M+H]^+$=532.15.

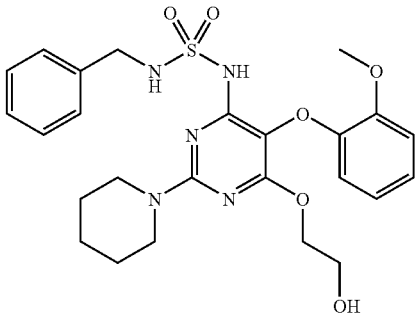
f) Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl]-amide (Example 206) (40 mg) {LC-MS: t_R=5.63; $[M+H]^+$=690.50} was prepared accoridng to the procedure described in Examples 5, 12 and 14 from benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl]-amide (Example 205) (50 mg).

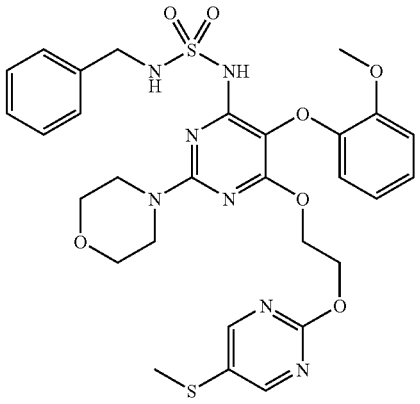
According to the procedures described for the preparation of Examples 203–206, the following compounds can be prepared:

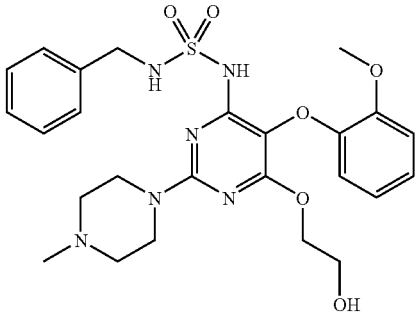


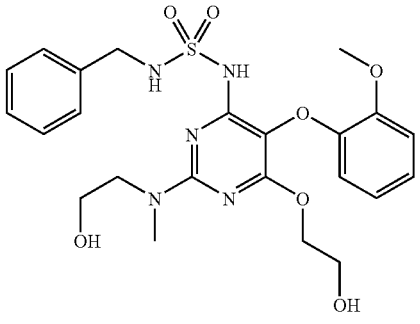


-continued

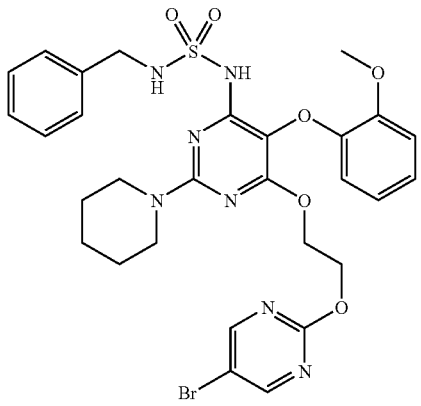






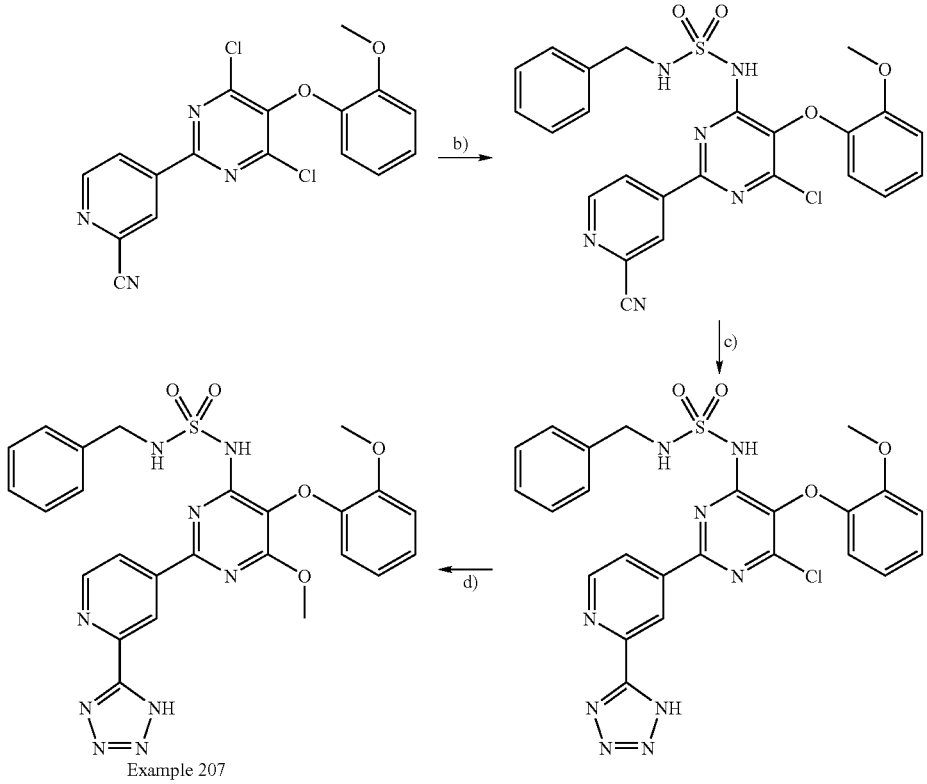


-continued



The preparation of compounds by the above described procedures is not limited to the molecules schematically depicted. Further variations, especially also in the sulfamide part of the molecule, can be achieved via the same pathway.

Example 207



Example 207

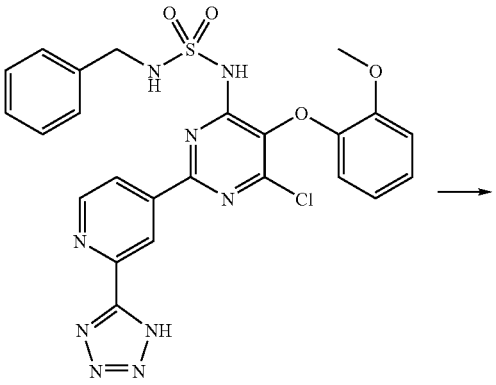
a) 4-[4,6-Dichloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine-2-carbonitrile can be prepared as described in WO 96/19459 and WO 00/42035.

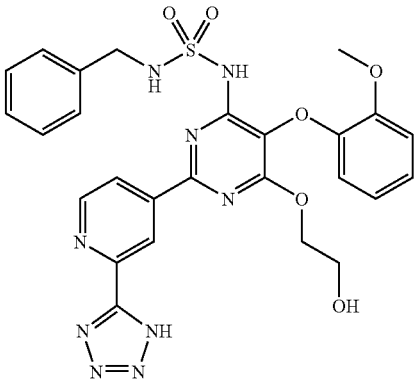
b) 4-[4,6-Dichloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine-2-carbonitrile (3.2 g) was dissolved in DMSO (20 ml), N-ethyidiisopropylamine (1.7 ml) and benzylsulfamic acid amide potassium salt (3.52 g) was added. The mixture was stirred for 18 h at rt, poured onto ice/water, acidified with solid citric acid and the precipitate was filtered off and recrystallized form EtOAc to give benzylsulfamic acid [6-chloro-2-(2-cyano-pyridin-4-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (4.17 g). LC-MS: t_R=5.55; $[M+H]^+$=523.29.

c) Benzylsulfamic acid [6-chloro-2-(2-cyano-pyridin-4-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (4.17 g) was dissolved in DMF (55 ml). Sodium azide (5.2 g) and ammonium chloride (4.28 g) were added and the mixture was stirred for 20 h at 80° C. Then the mixture was pored onto water and extracted with EtOAc. The layers were separated and the water layer was acidified with acetic acid to pH ~5 and extracted with EtOAc. The combined organic layers from the 2nd extraction were washed with brine, dried over magnesium sulfate, filtered and evaporated. The crude material was purified by chromatography over silicagel with EtOAc/MeOH/ammonia=5/1/0.5 to give benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (1.67 g). LC-MS: t_R=5.02; $[M+H]^+$=566.36.

d) According to the procedures described in Examples 1, 8 and 9, benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl}-amide (150 mg) was transformed to benzylsulfamic acid [6-methoxy-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (50 mg) (Example 207). LC-MS: t_R=4.84; $[M+H]^+$=562.29.

Example 208

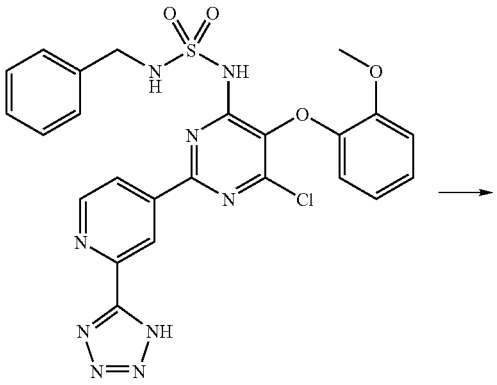




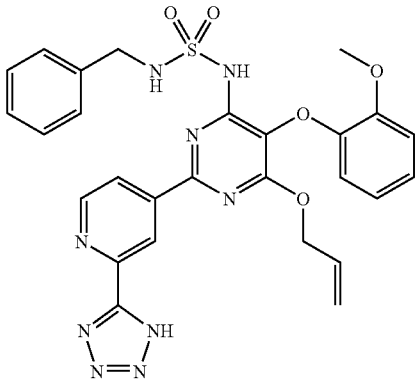
Example 208

Benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (1.5 g) was prepared according to the procedure described in Example 207d. LC-MS: t_R=4.28; $[M+H]^+$=592.63.

Example 209



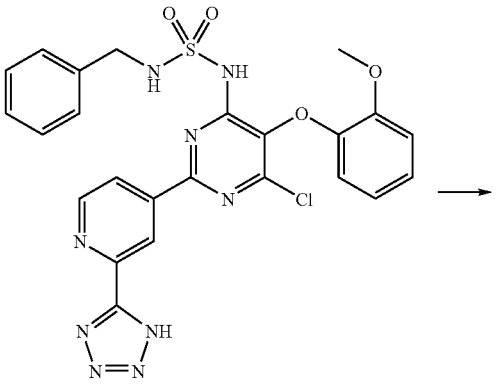
-continued

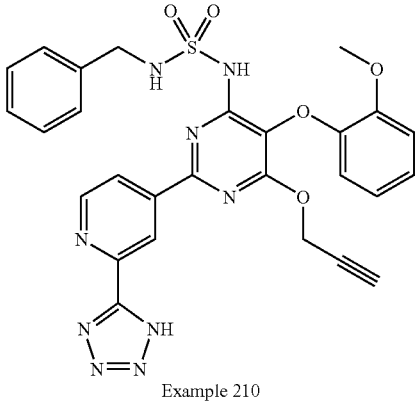


Example 209

Benzylsulfamic acid [6-allyloxy-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (94 mg) was prepared according to the procedure described in Example 207d. LC-MS: t_R=4.96; $[M+H]^+$=588.70.

Example 210

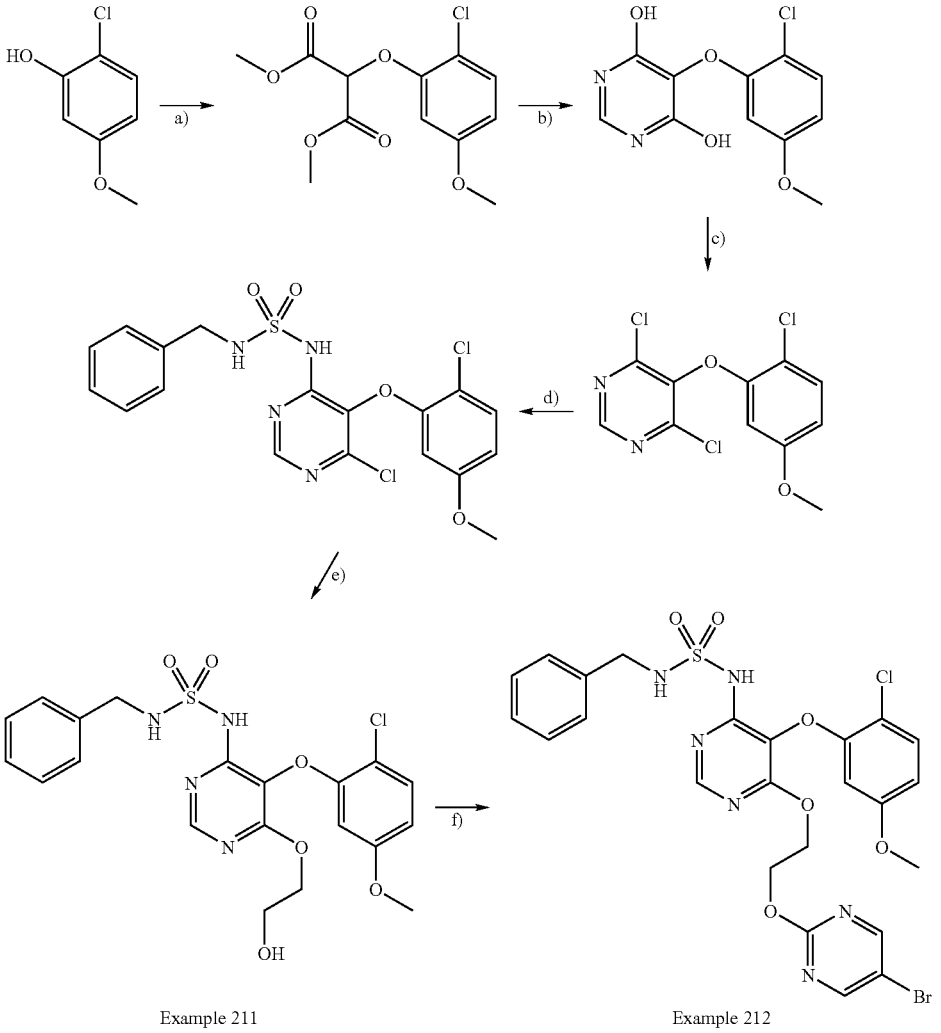




Example 210

Benzylsulfamic acid [5-(2-methoxy-phenoxy)-6-prop-2-ynyloxy-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (100 mg) was prepared according to the procedure described in Example 207d. LC-MS. t_R=4.77; $[M+H]^+$=486.51.

Example 211–212



Example 211 Example 212

2-Chloro-5-methoxy-phenol was prepared according to procedures described in the literature [M. Julia, J. de Rosnay; *Chimie Thérapeutique*, 1969, 4, p 334–343.]

a) 2-Chloro-5-methoxy-phenol was reacted with chloro dimethyl malonate in acetone and potassium carbonate according to the procedure described in Referential Example 1b to give 2-(2-chloro-5-methoxy-phenoxy)-malonic acid dimethyl ester.

b) 5-(2-Chloro-5-methoxy-phenoxy)-pyrimidine-4,6-diol was prepared from 2-(2-chloro-5-methoxy-phenoxy)-malonic acid dimnethyl ster and formamidine hydrochloride according to the procedure described in Referential Example 1c.

c) 4,6-Dichloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidine was prepared from 5-(2-Chloro-5-methoxy-phenoxy)-pyrimidine-4,6-diol according to the procedure described in Referential Example 3b. LC-MS: t_R=5.18; $[M+H]^+$=306.40; ^{1}H-NMR ($CDCl_3$): 8.7 ppm (s, 1H); 7.4 ppm (d, 1H); 6.6 ppm (d, 1H); 6.02 ppm (s, 1H); 3.86 ppm (s, 3H).

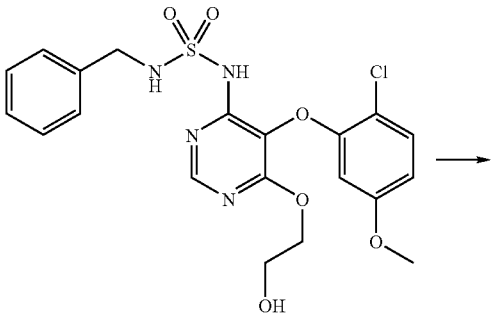
d) Benzylsulfamic acid [6-chloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (0.7 g) was prepared from 4,6-dichloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidine (1 g) and benzylsulfamic acid amide potassium salt (1.21 g) according to the procedure described in Referential Example 15. LC-MS: t_R=5.13; $[M+H]^+$=456.91.

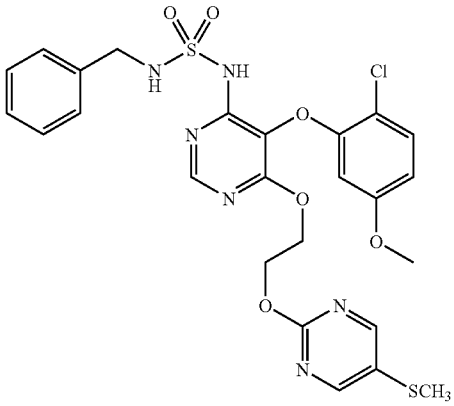
e) Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-amide (0.6 g) (Example 211) was prepared from benzylsulfamic acid [6-chloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (0.697 g) according to the procedure described in Example 3,10 or 13. LC-MS: t_R=4.50; $[M+H]^+$=481.12.

f) Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (77 mg) (Example 212) was prepared from benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-amide (120 mg) (Ex-

ample 211) and 5-bromo-2-chloropyrimidine (100 mg) according to the procedure described in Example 14. LC-MS: t_R=5.29; $[M+H]^+$=639.04.

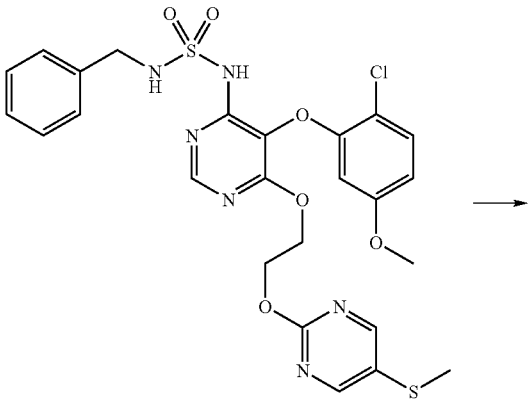
Example 213



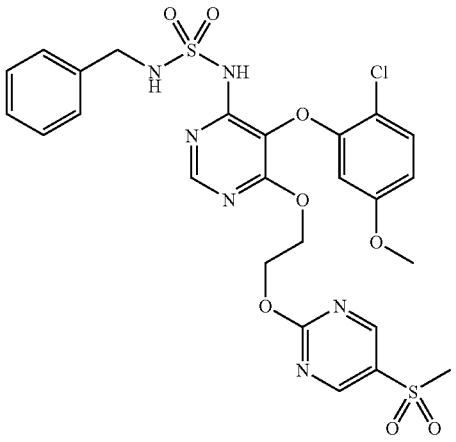


Benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (138 mg) (Example 213) was prepared from benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-amide (240 mg) (Example 211) and 5-methylsulfanyl-2-chloropyrimidine (180 mg) according to the procedure described in Example 14. LC-MS: t_R=5.22; $[M+H]^+$=606.75.

Example 214

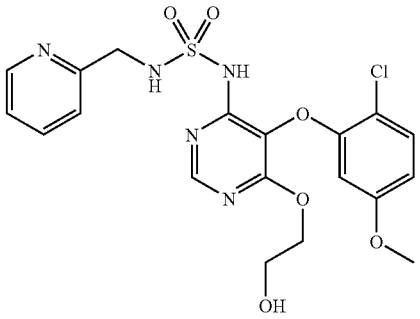


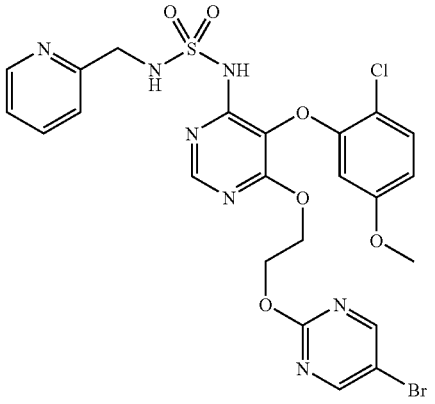
-continued



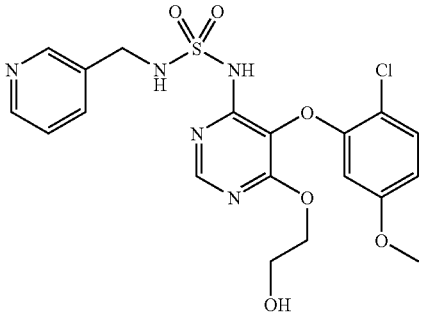
Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-methanesulfonyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide (47 mg) (Example 214) was prepared by oxidation of benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxyl]-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (80 mg) (Example 213) with peracetic acid according to general procedures described in the literature. LC-MS: t_R=4.72; $[M-H]^+$=635.05.

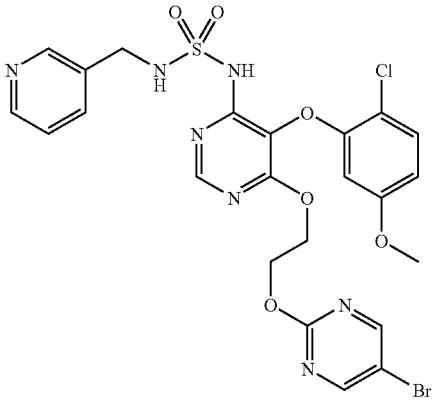
According to the procedures described for the preparation of Examples 211–214, the following compounds can be prepared:



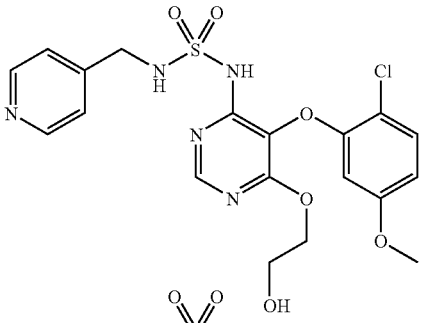


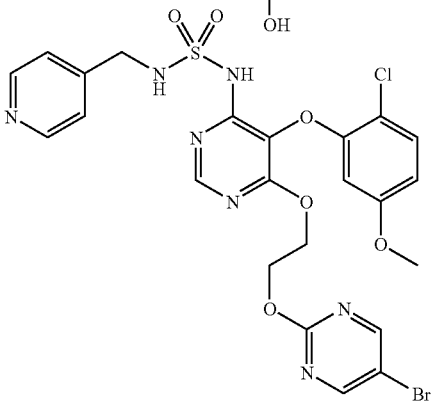
-continued





-continued



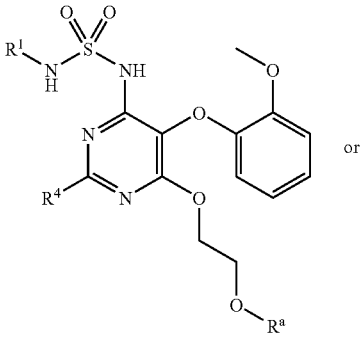


The preparation of compounds by the above described procedures is not limited to the molecules schematically depicted. Further variations, especially in the sulfamide-part and at the side chain in position 6 of the core pyrimidine ring of the molecule, can be achieved via the same pathway.

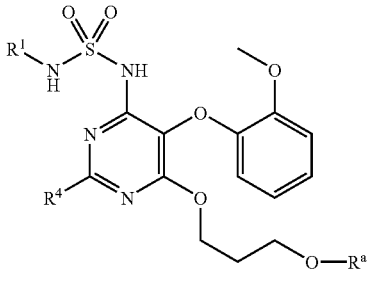
Example 215

Using methods described in the above Examples and in Schemes 1 to 4 and the cited references, the compounds disclosed in Table a) can be prepared:

TABLE a



or



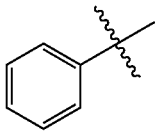
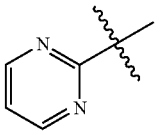
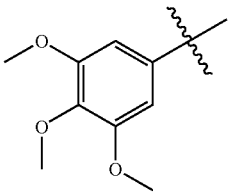
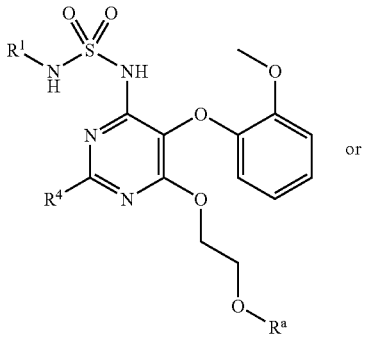
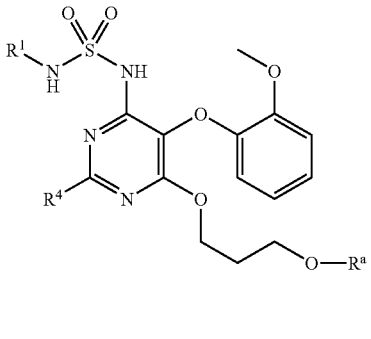
R^1:	R^a:	R^4:
		

TABLE a-continued



or



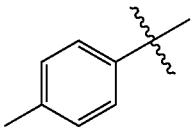
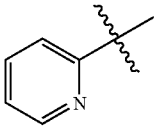
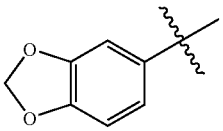
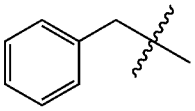
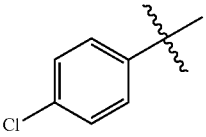
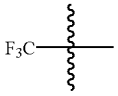
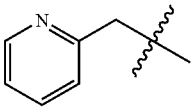
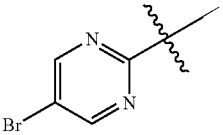
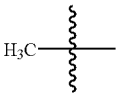
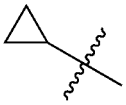
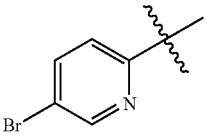
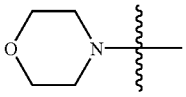
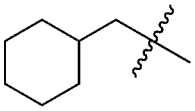
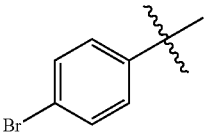
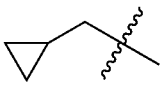
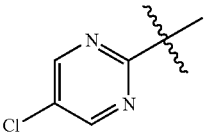
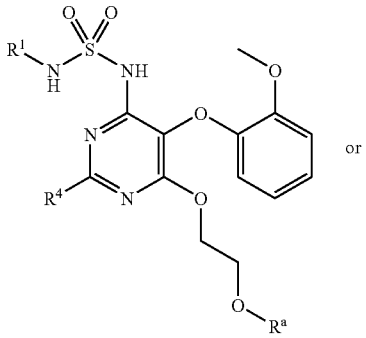
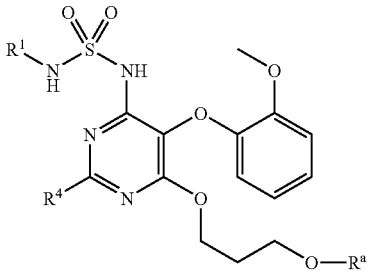
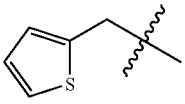
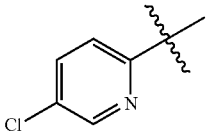
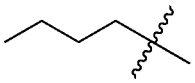
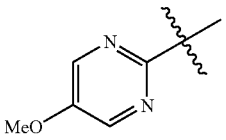
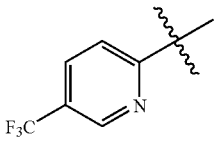
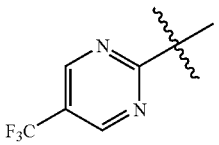
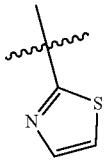
R^1:	R^a:	R^4:
		
		
		
		
		
		

TABLE a-continued



or



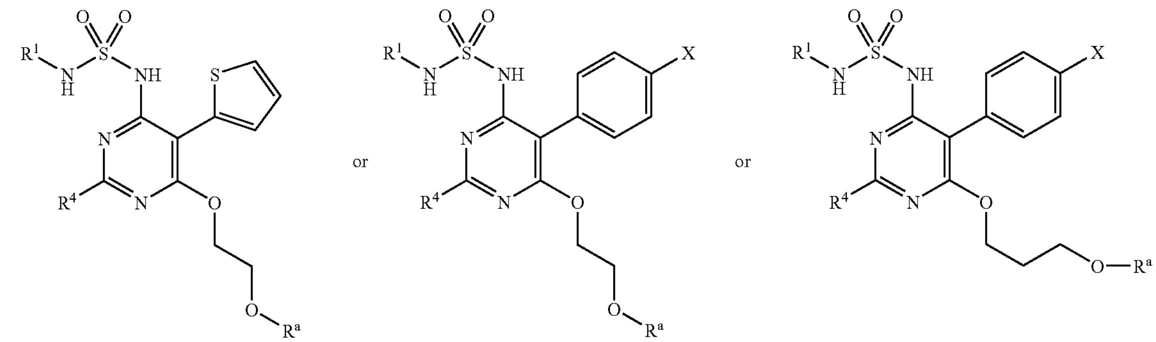
R^1:	R^a:	R^4:
		
		
		
		
		

 indicates the connection of the substituents to the respective atom of the core unit

Example 216

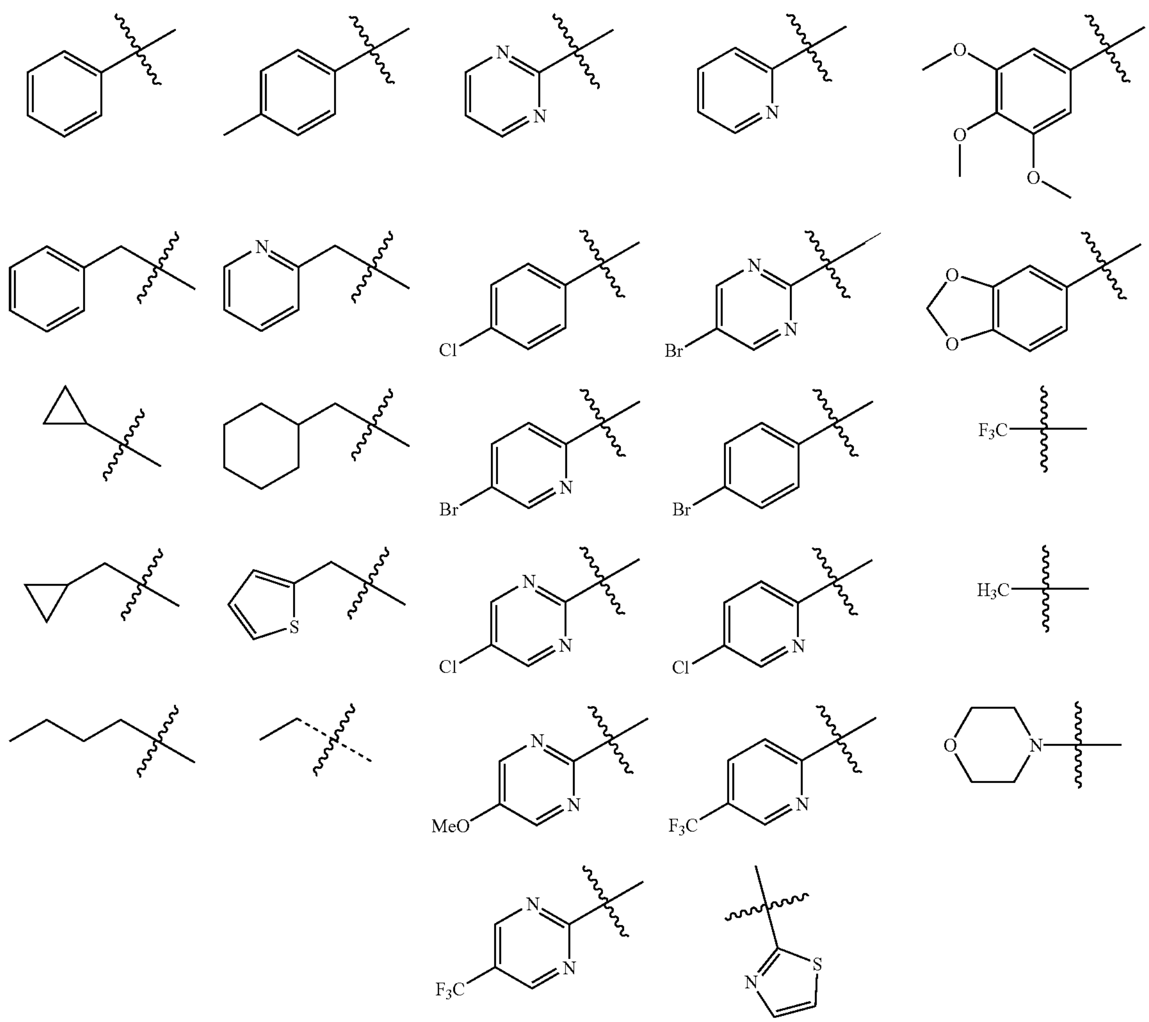
Using methods described in the above Examples and in Schemes 1 to 4 and in the cited references, the compounds disclosed in Table b) can be prepared:

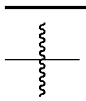
TABLE b



X = H; CH_3; Cl; Br; OCH_3; F; CF_3; CH_2CH_3

R[1]:	R[a]:	R[4]:

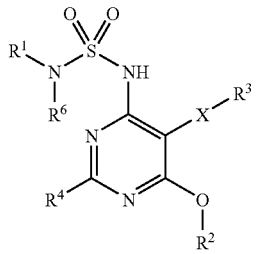



indicates the connection of the substituents to the respective atom of the core unit

What is claimed is:

1. A compound of general formula I

General Formula I



or an optically pure enantiomer or diastereomer, a mixture of enantiomers or diastereomers, a diastereomeric racemate, a mixture of diastereomeric racemates or a meso-form or a pharmaceutically acceptable salt thereof;

wherein

R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; or hydrogen;

R^2 represents $—CH_3$; $—(CH_2)_n—Y—R^a$; $—(CH_2)_m—C{\equiv}C—(CH_2)_p\text{-}Z\text{-}R^a$; $—(CH_2)_k—C(R^b){=}CR^cR^d$; or $—CH_2$-tetrahydrofuran-2-yl;

R^3 represents aryl; or heteroaryl;

R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxylower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N (lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; heteroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy; heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocyclyl-lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; or cycloalkylsulfinyl;

R^6 represents hydrogen; or lower alkyl;

X represents oxygen; sulfur; $—CH_2—$ or a bond;

Y represents a bond, —O—; —NH—; $—NH—SO_2—$; $—NH—SO_2—NH—$; O—CO—; —CO—O—; —O—CO—NH—; —NH—CO—O—; or —NH—CO—NH—;

Z represents oxygen or a bond;

k represents 1, 2, 3, 4, 5 or 6;

n represents 2, 3, 4, 5 or 6;

m represents 1, 2, 3, 4 or 5;

p represents 0 (zero), 1, 2 or 3 and if p represents 0 (zero), Z cannot represent oxygen;

R^a represents aryl; heteroaryl; lower alkyl; cycloalkyl; or hydrogen;

R^b and R^c independently represent hydrogen or lower alkyl; and

R^d represents hydrogen; lower alkyl; aryl; or heteroaryl.

2. The compound according to claim **1** or a pharmaceutically acceptable salt thereof;

wherein

R^1, R^2 and R^4 are as above;

X represents oxygen; and

R^3 represents phenyl or mono-substituted phenyl substituted with halogen, lower alkyl, lower alkoxy or lower alkanoyl.

3. The compound according to claim **1** or a pharmaceutically acceptable salt thereof

wherein

R^1 and R^4 are as above;

X represents oxygen;

R^3 represents phenyl or monosubstituted phenyl substituted with lower alkoxy;

R^2 represents $—(CH_2)_n—Y—R^a$; and

n, Y and R^a are as defined in general formula I.

4. The compound according to claim **1** or a pharmaceutically acceptable salt thereof

wherein

R^1 and R^4 are as above;

X represents oxygen;

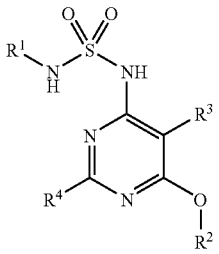
R^3 represents phenyl or monosubstituted phenyl substituted with lower alkoxy; and

R^2 represents $—(CH_2)_2—O—R^a$,

wherein R^a is as defined in general formula I in claim **1**.

5. A compound of formula II

Formula II



or an optically pure enantiomer or diastereomer, a mixture of enantiomers or diastereomers, a diastereomeric racemate, a mixture of diastereomeric racemates or a meso-form or a pharmaceutically acceptable salt thereof;

wherein

R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; or hydrogen;

R^2 represents $—CH_3$; $—(CH_2)_n—Y—R^a$; $—(CH_2)_m—C{\equiv}C—(CH_2)_p\text{-}Z\text{-}R^a$; $—(CH_2)_k—C(R^b){=}CR^cR^d$; or $—CH_2$-tetrahydrofuran-2-yl;

Y represents a bond, —O—; —NH—; $—NH—SO_2—$; $—NH—SO_2—NH—$; O—CO—; —CO—O—; —O—CO—NH—; —NH—CO—O—; or —NH—CO—NH—;

R^a represents aryl; heteroaryl; lower alkyl; cycloalkyl; or hydrogen;

Z represents oxygen or a bond;

k represents 1, 2, 3, 4, 5 or 6;

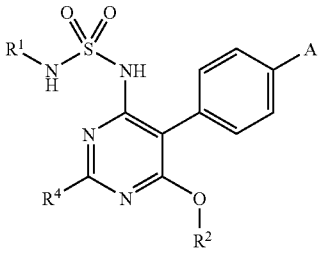
R^b and R^c independently represent hydrogen or lower alkyl; and

R^d represents hydrogen; lower alkyl; aryl; or heteroaryl;

n represents 2, 3, 4, 5 or 6;
m represents 1, 2, 3, 4 or 5;
p represents 0 (zero), 1, 2 or 3 and if p represents 0 (zero), Z cannot represent oxygen;
R^3 represents aryl; or heteroaryl; and
R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxylower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N (lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; heteroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy; heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocyclyl-lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; or cycloalkylsulfinyl.

6. A compound of formula III

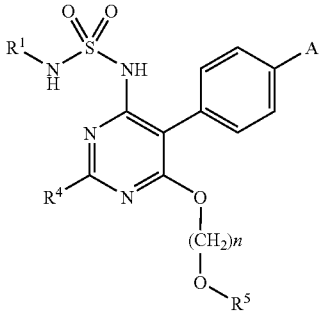
Formula III



or an optically pure enantiomer or diastereomer, a mixture of enantiomers or diastereomers, a diastereomeric racemate, a mixture of diastereomeric racemates or a meso-form or a pharmaceutically acceptable salt thereof;
wherein
R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocydyl-lower alkyl; lower alkyl; or hydrogen;
R^2 represents $—CH_3$; $—(CH_2)_n—Y—R^a$; $—(CH_2)_m—C{\equiv}C—(CH_2)_p\text{-}Z\text{-}R^a$; $—(CH_2)_k—C(R^b){=}CR^cR^d$; $—CH_2$-tetrahydrofuran-2-yl;
k represents 1, 2, 3, 4, 5 or 6;
p represents 0 (zero), 1, 2 or 3 and if p represents 0 (zero), Z cannot represent oxygen;
m represents 1, 2, 3, 4 or 5;
n represents 2, 3, 4, 5 or 6;
Y represents a bond, —O—; —NH—; $—NH—SO_2—$; $—NH—SO_2—NH—$; O—CO—; —CO—O—; —O—CO—NH—; —NH—CO—O—; or —NH—CO—NH—;
R^a represents aryl; heteroaryl; lower alkyl; cycloalkyl; or hydrogen;
Z represents oxygen or a bond;
R^b and R^c independently represent hydrogen or lower alkyl;
R^d represents hydrogen; lower alkyl; aryl; or heteroaryl;
R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxylower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N (lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; heteroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy; heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocyclyl-lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; or cycloalkylsulfinyl; and
A represents hydrogen, methyl, ethyl, chlorine, bromine, fluorine, trifluoromethyl or methoxy.

7. A compound of formula IV

Formula IV



or an optically pure enantiomer or diastereomer, a mixture of enantiomers or diastereomers, a diastereomeric racemate, a mixture of diastereomeric racemates or a meso-form or a pharmaceutically acceptable salt thereof;
wherein
R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; or hydrogen;
R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxylower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N (lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; het-

eroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy; heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocyclyl-lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; or cycloalkylsulfinyl

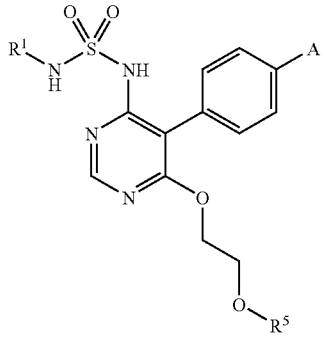
n represents 2, 3, 4, 5 or 6;

A represents hydrogen, methyl, ethyl, chlorine, bromine, fluorine, trifluoromethyl or methoxy; and

R^5 represents hydrogen, lower alkyl, aryl, heteroaryl or cycloalkyl.

8. A compound of formula V

Formula V



or an optically pure enantiomer or diastereomer, a mixture of enantiomers or diastereomers, a diastereomeric racemate, a mixture of diastereomeric racemates or a meso-form or a pharmaceutically acceptable salt thereof;

wherein

R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; or hydrogen;

A represents hydrogen, methyl, ethyl, chlorine, bromine, fluorine, trifluoromethyl or methoxy; and

R^5 represents hydrogen, lower alkyl, aryl, heteroaryl or cycloalkyl.

9. The compound according to claim **8** or an optically pure enantiomer or diastereomer, a mixture of enantiomers or diastereomers, a diastereomeric racemate, a mixture of diastereomeric racemates or a meso-form or a pharmaceutically acceptable salt thereof;

wherein R^5 in Formula V represents heteroaryl.

10. The compound according to claim **1**, being:

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(4-methoxy-benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Benzylsulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid-[5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-methylsulfan-yl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-2-pyridin-4-yl-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-2-pyridin-4-yl-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-py(imidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

or a pharmaceutically acceptable salt thereof.

11. The compound according to claim **1**, being:

Pyridin-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-py(midin-2-yloxy-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	7,094,781
(45)	ISSUED	:	August 22, 2006
(75)	INVENTOR	:	Martin Bolli et al.
(73)	PATENT OWNER	:	Actelion Pharmaceuticals Ltd.
(95)	PRODUCT	:	OPSUMIT® (macitentan)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 7,094,781 based upon the regulatory review of the product OPSUMIT® (macitentan) by the Food and Drug Administration. According to United States Patent and Trademark Office records, the original expiration date of the patent as of the date of issuance of this certificate is October 12, 2022. Because it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,150 days

subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 15th day of March 2018.

Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office